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Center for Biologics Evaluation and Research

104th Meeting of the Blood Products Advisory Committee

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P R O C E E D I N G S (8:00 a.m.)

Agenda Item: Call to Order and Opening Remarks

DR. HOLLINGER: Thank you all for being here today. The topic for today is considerations for strategies to further reduce the risk of bacterial contamination in platelets. A very interesting topic, a very important issue and I am sure we are going to have lots of discussion today.

With that, I think we have an award to present. I think Dr. Epstein has it.

DR. EPSTEIN: Good morning, everyone. It is my privilege and bittersweet pleasure to present an award to Dr. Andrea Troxel, who is an outgoing member of the BPAC. Dr. Troxel is a professor of biostatistics at the Perelman School of Medicine, University of Pennsylvania. She has been a distinguished member of this committee since 2008.

We have tried to make your academic career interesting by inviting you to participate in discussions on many topics, but just to cite a few, Xenotrophic murine leukemia virus, related human retrovirus, measures to preserve the blood supply in severe emergencies, evaluation of the safety and effectiveness of the OraQuick in-home HIV test, testing of source plasma for Hepatitis B by nucleic acid, and discussions of dangi virus, and that is just mentioning a few.

If you'd be kind enough to join me up here, I would like to present you with a plaque and a certificate to thank you. I hope that you will stay close to us. We often invite back our members as special government employees for temporary voting. It has been a pleasure working with you.

DR. HOLLINGER: I was thinking about talking to my wife last night, and she told me when I came home, there was a lot of work I had to do at home. I told you the Phyllis Diller thing the other day, and she said, housework can't kill you, but why take the chance.

Let's go around the committee again, introduce yourselves, where you are from, and so on. Tony, could you start again, please?

DR. BONILLA: Tony Bonilla, Boston Children's Hospital.

DR. DEMETRIADES: Demetrios Demetriades, USC School of Medicine Los Angeles.

DR. DI MICHELE: Donna DiMichele, Division of Blood Diseases and Resources, National Heart, Lung and Blood Institute

DR. GILCHER: Ron Gilcher, Fort Meyers, Florida, now consulting hematologist.

DR. KEY: Nigel Key, hematology, UNC Chapel Hill.

DR. LINDEN: Jean Linden, Blood and Tissue Sources, New York State Department of Health.

MS. TROXEL: Andrea Troxel, Perelman School of Medicine, University of Pennsylvania.

DR. MAGUIRE: James Maguire, Brigham and Women's Hospital in Boston.

DR. PIPE: Steve Pipe, Pediatrics and Pathology, University of Michigan.

DR. RHEE: Peter Reed, Department of Surgery, University of Arizona.

DR. ANDERSON: Karen Anderson, Division of Health Care Quality Promotion at the Centers for Disease Control.

DR. BIANCO: Celso Bianco with America’s Blood Centers.

MR. DUBIN: Corey Dubin, Santa Barbara, California, Committee of Ten Thousand. I am the end user representative at the table.

DR. SCHEXNEIDER: Katherine Schexneider, Blood Services, Walter Reed, Bethesda.

DR. ALVING: Barbara Alving, formerly NIH, consulting hematologist.

DR. BECKER: Joanne Becker, Roswell Park Cancer Institute.

DR. ROSEFF: Sue Roseff, Virginia Commonwealth University in Richmond.

DR. STRONCEK: Dave Stroncek, Department of Transfusion Medicine, NIH Clinical Center.

LCDR EMERY: Bryan Emery designated federal official.

Agenda Item: Conflict of Interest Statement

LCDR EMERY: At this time, I am going to read the conflict of interest statement for September 21st, 2012. This brief announcement is in addition to the conflict of interest statement read at the beginning of the meeting on September 20th, 2012, and will be part of the public record for the Blood Products Advisory Committee Meeting on September 21st.

The committee will discuss considerations for strategies to further reduce the risk of bacterial contamination in platelets. This is a particular matter involving specific parties. In addition, the committee will hear an update on the September 6th and 7th, 2012, FDA workshop on risks and benefits of hydroxyl starch solutions. There is no conflict of interest involved in this committee update.

Based on the agenda and all financial interests reported by members and consultants, no conflict of interest waivers were issued under 18 USC 208 and 712 of the Food, Drug and Cosmetic Act. With regards to FDA's guest speakers, the agency has determined that the

information provided is essential. The following information is being made public to allow the audience to objectively evaluate any presentation and/or comments.

Dr. Michael Jacobs and Dr. Larry Dumont each have associations with several firms that could be affected by the committee discussions. Dr. Celso Bianco is serving as the industry representative, acting on behalf of all related industry. Dr. Bianco is employed by America's Blood Centers in Washington, D.C. Industry representatives are not special government employees and do not vote.

There may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. This conflict of interest statement will be available for review at the registration table.

We would like to remind members and participants that if the discussions involve any other products or firms not already on the agenda, for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their

exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any firms, its products, and if known, its direct competitors. Thank you.

Topic III: Considerations for Strategies to Further Reduce the Risk of Bacterial Contamination in Platelets

DR. HOLLINGER: Thank you, Bryan. We will start today with Dr. Haddad, who is going to give us an overview, an option for consideration. There is a timer up here, so please pay attention to it. It has your time limit on it. When the yellow light comes on, you have two minutes to sort of summarize, and the red to complete your discussions.

Agenda Item: Overview and Options for Consideration, Salim Haddad, M.D., FDA

DR. HADDAD: This morning, I am going to present to you with an overview of the topic of bacterial contamination of platelets, and with options to consider to further reduce this risk in platelets. First, I am going to start with the background on platelet components and bacterial platelet contamination. Then, I will detail the current strategies for bacterial detection in transfused platelets in the U.S. Then, I will describe the residual risk of bacterial contamination in transfused platelets. I

will conclude with potential strategies to improve platelet safety from bacterial contamination.

As you know, platelets are blood cells that serve to prevent or stop bleeding. About 2 million platelets are transfused annually in the United States, 88 percent of which are apheresis, also known as single donor platelets. The rest are whole blood derived platelets, which can be pulled either early on, using an FDA-approved pulling system, or toward the end of the storage, within four hours prior to transfusion.

All blood components are susceptible to bacterial contamination. However, platelets, because they are stored at room temperature, are uniquely vulnerable to bacterial outgrowth during storage. The main source of bacterial contamination is the donor skin flora. Contamination could also arise from asymptomatic donor bacteria or during processing of the unit.

The current strategies in place to mitigate the risk from bacterial contamination include donor health screening, a skin disinfection methods, diversion of an initial aliquot, visual inspection and bacterial detection. Some historical milestones is platelet shelf life, and these are intimately related to the issue of bacterial contamination of platelets. In 1984, the shelf life was extended from five to seven days only to be shortened back

to five days two years later, based upon reports of increased septic transfusion reactions in the recipient.

In 2002, FDA cleared the culture-based bacterial detection device for testing platelets. In 2004, the AABB implemented a standard to limit and detect bacterial contamination in all platelet components. That eventually led to the culture of apheresis platelets on the one, day zero being the day of collection.

In 2005, with the FDA clearance of seven-day containers for apheresis platelets, the shelf life was extended to seven days, but only for those centers participating in the PASSPORT study. As part of the study, apheresis platelets were cultured on day one, and outdated seven-day platelets were retested by culture.

The study was designed to establish with 95 percent confidence that the detectable contamination rate of expired seven-day platelets was equal or less to one in 5000. The one in 5000 rate that was the bacterial detection rate on day one, based on the best available data at the time, and represented a minimal estimate of the contamination rate of five-day uncultured platelets, which was the standard product at the time.

In 2008, the PASSPORT study was terminated early for futility and interim analysis having shown a contamination rate of expired seven-day platelets too high

to meet the pre-specified end point of equal or less than one in 5000 with 95 percent confidence. The seven-day platelets were no longer available in the U.S.

The FDA cleared bacterial detection devices fall in two main categories, cultural-based and rapid test, also known as point of care or point of issue tests. In term of the culture-based test, two have been approved by FDA, the BacT/ALERT from BioMerieux and eBDS from Pall. The BacT/ALERT system has both aerobic and anaerobic bottles, whereas the eBDS has only an aerobic pouch.

Both devices have been cleared for quality control indication, based on two elements. Number one, experimental spiking studies to determine the analytical sensitivity of the device. Also, on the absence of determination of clinical sensitivity and specificity. I will elaborate on the spiking studies later on in my presentation.

The analytical sensitivity for both devices was set at one to 10 cfu per ml, and sampling occurs at least 24 hours after platelet collection. While clear for QC testing, this culture-based devices actually are being used by most collection centers, de facto as recessed to determine the suitability for transfusion, prior to shipment to hospitals.

The exact sampling and cultural procedures, they vary among blood collection centers. A sampling is occurring at least 18 hours post-collections, commonly at 24. Products are made available for transfusion after a variable hold period from less than six hours to greater than 24, and released as negative to date if tested by the bacterial system.

The performance of the culture-based devices on clinical product has been evaluated by a number of studies. Among those studies, the PASSPORT study and the bacterial surveillance programs of the American Red Cross blood systems and Canadian blood services. What these four studies have in common is that they tested apheresis platelets on day one, using the BacT/ALERT system.

I will first describe the methodology, and then I will give you the results from these studies. The PASSPORT study used both aerobic and anaerobic bottles. The other studies used aerobic bottles only. PASSPORT sample 4 ml throughout the study in each bottle. The remaining studies, they doubled the sampling volume from about 4 ml to about 8 ml during the course of this surveillance. The American Red Cross converted to 100 percent use of diversion pouch during the course of surveillance. The other studies used diversion throughout.

In term of the results, this is the spectrum of findings from these different results. The number of platelet collections tested varied from 210,000 to 3.4 million. The day one through positive rate varied from 1 in 4300 to about 1 in 8400. If you combine all of the numerators and denominators, just to have a broad idea about the grade, it was about one in 5300. The majority of bacterial organisms were gram positive, from 71 percent to 87 percent. The rest were obviously gram negative. The false positive rate ranged from 1 in 4300 to 1 in 500. The false positive over a true positive ratio from 2 to 8.

This is the second series of studies, address the issue of the clinical sensitivity of the day one culture, and the residual risk of bacterial contamination in outdated platelets. The studies in question here, we have the PASSPORT study again, and the studies from the Irish Blood Transfusion Service and the Welsh Blood Service. Dr. William Murphy, from the Irish Blood Transfusion Service is with us today. He will be presenting the experience of his service later on this morning.

Again, methodology first. PASSPORT tested apheresis platelets, whereas the other two studies, they tested apheresis and buffy-coat pools, all used the BacT/ALERT, aerobic and anaerobic bottles. All tested on day one and on outdate. For the PASSPORT and the Welsh

study, the outdate was on the 8th because they were dealing with seven-day platelets. The outdate for the Irish study was either day six or day eight, because their platelets were either day five or day seven. The Irish study additionally tested on day four.

In term sampling, PASSPORT sampled 24 to 36 hours after collection, 4 ml times 2 from the mother collection bag. The sampling protocol for the Welsh and Irish studies were similar sampling, apheresis on average 16 to 17 hours after collection, and pools at least 30 hours after collection, using about 8 to 10 ml, sampling volumes times two. However, the Welsh study sampled from the mother collection bag, whereas the Irish study sampled from each split product coming of the mother collection bag.

The range of results, the number of platelet collections tested varied from 43,000 to about 400,000. The day one through positive rate ranged from 1 in 4300 to 1 in 1500. The day four through positive rate, 1 in 3300. The outdate through positive rate ranged from 1 in 1000 to 1 in 1500 with the majority of organism being gram positive. The clinical sensitivity of the day one culture was from 22 to 40 percent. The clinical sensitivity of day one culture that represents the detection efficiency of a day one culture.

Now, this is a study on the residual risk of bacterial contamination on the day of transfusion. In this study, over 27,000 apheresis platelets that had tested negative by day one culture were retested on the day of transfusion, with the rapid PGD test and with traditional culture. Twelve cultured positive units were identified in the study for a bacterial detection rate of one in 2300 units approximately, and all were gram positive organisms.

This was a study that Dr. Michael Jacobs was the principle investigator on. Again, he is with us today and he will be presenting the study in full details. This is a summary table, summarizing the findings from the study I just presented. The core elements that take away from this table is that the true positive rate on day one, the day one culture is able to pick up a number of contaminated units at the rate ranging from 1 in 1500 to 1 in 8400.

Number two, there is a residual risk at transfusion time and at outdate, ranging from about 1 in 2300 to about 1 in 1000, that the majority of the residual risk is associated with gram positive organisms. This underscores the relative effectiveness of the day one culture in intercepting the gram negative organisms on day one. However, the day one culture was able to pick up only from about 22 to 40 percent of the contaminations. That

means, it is missing between 60 and 80 percent of the contaminations on day one.

That was the contamination rate in the clinical products. How about the impact clinically on patients receiving those platelets. This slide and the next one has the sepsis and fatality outcomes associated with transfusion of apheresis platelets, as reported by passive haemovigilance reports from the American Red Cross and the Canadian Blood Services. By passive haemovigilance, we mean that the reports of transfusion reactions were initiated by the clinical team, only and if they recognized and diagnose the septic transfusion reactions, and that is not always the case.

The Red Cross haemovigilance data covered a five-year period. About 4 million platelets were distributed during that period. They registered 38 septic transfusion reactions for a rate of about 1 in 100,000. There were 35 out of the 38 septic reactions were due to gram positive organisms. There were four fatalities for a rate of about one in a million per distributed product.

The Canadian Blood Services reported on a seven-year period, about 210,000 collections. There were two septic transfusion reactions, one gram negative, one gram positive, for a rate of about one in 100,000. The gram negative contamination led to a fatality for a rate of one

in about 210,000 collections. You see the numerator is one and it is always difficult to interpret the results with a numerator of one. There was no confidence interval around it.

These two surveillance programs were passive surveillance, how does active surveillance differ from passive surveillance? This is a study conducted by Dr. Jacobs and Yomtovian at Cleveland. In this active surveillance programs, the platelets were cultured prior to transfusion. The transfused patients were followed for evidence of a transfusion reaction. If you look at the second row, the bacterial contamination rates, if you compare active versus passive surveillance, the active surveillance had 32 times higher the rate of bacterial contamination compared to passive. The septic transfusion reactions were 10 times higher by active surveillance, compared to passive surveillance.

These are the fatalities reported to FDA, associated with bacterial contamination of platelets. This is a comparison between two periods, 1995 to 2004, and 2007 to 2011. The first period had 60 reports of fatalities related to bacterial contamination of platelets, and the second period, 14. If you look at the average number of total fatalities per year, these are the blue bars, you

notice there are decrees from an average of six in the first period, and an average of 2.8 in the second period.

This decrease can be contributed to the number of measures that were introduced to decrease the bacterial contamination, and these include the day one culture, the improved methods for skin disinfection, and also the introduction of the diversion pouch. The decrease affected essentially the gram negative organism, which decreased from 3.8 average in the first period to 1 in the second period. However, it did not impact significantly the gram positive, which decreased from 2.2 to 1.8.

These are the same data distributed by gram negative or gram positives. You notice that in the first period, the gram negative were about two-thirds of the fatalities, and the gram positive about one-third. This distribution was reversed in the second period, gram negative one-third, gram positive two-thirds. Again, this is another evidence of the relative sensitivity of the greater sensitivity of the day one culture in picking up the gram negative, which is the fast grower, compared to picking up the gram positives.

Moving onto the rapid detection tests, and these are non-culture based tests that provide results within 60 minutes. Two have been cleared by FDA, the PGD test from Verax and the BaxTx from Immunetics. This is the PGD test

from Verax. It is a qualitative, letter of law amino acid test. Its technology is based on the detection of lipopolysaccharide and Lipoteichoic acid antigens present on the surface of gram negative and gram positive bacteria, respectively. The readout is visual. It occurs at 20 to 60 minutes after sample application.

FDA initially cleared the PGD test in 2007, based on spiking studies, and it was cleared for testing apheresis platelets as an adjunct quality control test, following testing with an FDA-cleared culture-based device. The adjunctive labeling was based on the high limit of detection of the PGD test, 8.6 time 10 to the 5, compared to the culture-based device.

If I made well on this notion of limit of detection, limit of detection represents the bacterial contamination at which the device will give you a signal. The lower the limit of detection, the more sensitive the device. The limit of detection and analytical sensitivity go in opposite directions. The ultimate sampling time for the PGD test was set at greater than 72 hours post-collection, based on spiking studies.

In 2009, again based on spiking studies, the PGD test was cleared as a standalone QC test for platelets pooled within four hours prior to transfusion. These are the limit of detection results that were obtained by the

manufacturer, and formed the basis of the clearance, and these are the results that are currently in the package insert. The way spiking studies work is that each of 10 organisms that are traditionally associated with bacterial contamination of platelets are spiked in the platelet product. The bacterial concentration at which the device detects the organism sets the limit of detection for that organism. The overall limit of detection for the device is set by the highest limits of detection, and in this case, it was force of ratio 8.6 time 10 to the 5.

Now, subsequent published independent spiking studies have shown that the limits of detections for some organisms were higher in those independent studies than those established by the manufacturer. That means that the test was less sensitive in the hands of the subsequent studies than during the experiments conducted by the manufacturer.

In one study, the four staph epi and E. coli, the limits of detection was determined to be two logs higher than the ones established by the manufacturer. In another study for gram positive bacteria, staph aureus and bacillus subtilis, the limits of detection were in good agreement with the package insert. However, for gram negative bacteria, Klebsiella and E. coli, the limits of detection were two logs higher. As you know, the gram negatives are

the fast grower and considered the more pathogenic for patients.

This is another spiking study, where they conducted an inter-laboratory comparison of the detection of bacteria by the PGD test in 12 spiked platelet products. They had 12 spiked products. They took three samples out of each product, send them to three different laboratories. Each laboratory had a set of 12 samples, which were matched to the other 12 samples in the other two laboratories.

The PGD test detected four of 12 samples in each of the three laboratories, and they were the same matches samples. Eight were missed in each of the three laboratories, again, the same matched samples. Of those that were missed, four were below the manufacturer's limit of detection. Four were above it and they were supposed to be detected. Two of them were E. coli that was spiked at two different concentrations. The logs were one to three levels higher than the manufacturer's limit of detection. For the Klebsiella, it was slightly above the limit of detection on the package insert. For staph Auerus, it was two logs higher.

What might explain that variability between the limits of detection as established by the manufacturers, and by those investigators later on? One of the authors of the independent study hypothesized that the variability of

detection was due to an antigenic variation in the bacterial cell wall. In the second study, the author contacted Verax, and Verax indicated that the levels of detection were bacterial may vary, depending on the strain.

As a matter of fact, in the PGD post-marketing study, which I alluded to earlier, that was done on clinical platelet products, there was one PG false negative, meaning the PGD gave a negative result, but the culture was positive. That PGD false negative resulted from the lack of a specific antibody class in the PGD test.

In 2011, Verax provided FDA with the results of the post-marketing study, and the design was as follows. Apheresis platelets that had tested negative by culture. They were retested by the PGD test on the day of transfusion, using a repeat test strategy. The test was interpreted as repeatedly reactive, if two or greater out of three PGD tests were reactive. Otherwise, the test was interpreted as non-reactive.

In this study, over 27,000 apheresis platelet units were tested on the day of transfusion. Old reactive results were cultured, to determine true positive and false positive. The non-reactives were cultured only in a subset of about 10,424 units to determine true negative and false negative.

In the study, there were nine true positives that were identified by the PGD test, for a detection rate of about 1 in 3000. Therefore, the PGD test detected non-contaminated units on the day of transfusion that were missed by early culture. By comparison, the detection rate by early culture is about 1 in 5000, as I said earlier.

Other results from the post-marketing study, the false positive rate was .51 percent. That is based on the testing strategy of an initial reactive result. It was .91 percent based on initial reactive result. The false positive through true positive ratio was about 16, based on the repeat test strategy. By comparison, the BacT/ALERT false positive over true positive ratio was 2 to 8.

It is always concerning when you have false positive because that leads to the discard of otherwise suitable products, especially the much-needed HLA-matched or ABO-matched or fresh platelets. Also, false positive impacts disproportionately the small transfusion services which maintain small inventory. They receive their platelets on demand from their supplier.

In that same study, there were two false negative identified in the subset of 10,424 units. The approximate clinical sensitivity of the device was set at 60 percent. There were five cases detected by the culture, and the PGD detected only three, that is where the 60 percent came

from. Now, denominator of five, that is not a large number. The approximate clinical specificity was 99.3 percent. The invalid results rate was .48 percent.

Based on the detection by the PGD test on the day of transfusion of bacterial in apheresis platelets previously screened as negative by early culture, the adjunctive QC labeling was dropped, and a claim of safety measure when testing within 24 hours prior to transfusion was granted. That is for apheresis platelets previously screened by an early culture.

The 24 hour timeframe reflected the experimental conditions of the post-marketing study, and rendered possible batch testing of the platelet inventory of the day. Testing within that timeframe, even once a day, added safety to the five-day platelets. Labeling also included instruction to test as close as possible to transfusion time, with discussion on the potential effect of bacterial doubling time, between testing and transfusion. There were data on breakthrough bacteremia or clinical sepsis in face of a negative PGD test, also, data on the false negative results.

This is an additional clinical study to evaluate the performance of the PGD test. This was conducted at the University of Pittsburgh and at the Puget Sound Blood Center. Dr. Yazer was the main investigator and he is also

with us today. He will be presenting the details of the study. I would like just to highlight some of the results. The true positive rate was about 1 in 10,000, that's .01 percent. The false positive rate was about 1 in 300, that is .34 percent, for a false positive over true positive rate of 34. I should say that this study was conducted on non-leukocyte reduced whole blood-derived platelets pooled within four hours prior to transfusion.

The true positive rate was low, compared to previous study that were conducted on similar product. Previous study showed a contamination rate of .25 percent, so there was about 25 times lower detection rate by the PGD test on pooled whole blood-derived platelets.

The true positive contamination rate was about three times lower than the PGD detection rate in apheresis platelets in the study I just described to you. When traditionally, you expect the rate in pooled platelets to be 40 times higher than apheresis because of the multiplicity of the nation in a pooled product.

This is the other rapid test, cleared by FDA. It was cleared a few months ago for QC testing of leukocyte reduced whole blood-derived platelets, pooled within four hours prior to transfusion, again, based on spiking studies. Its technology is based on the detection of peptidoglycan. This is an ambiguous component of bacterial

cell walls, leading to an enzymatic reaction detected by a photometer. The readout is within 30 minutes of sample application, and the limit of detection by spiking studies was determined to be 5.8 times 10 to the 4. Currently, there are no published data on the performance of the BacT in clinical use.

This is the limit of detection studies by Immunetics. Again, same studies conducted like for the Verax, and the limit of detection in this case was 5.8 times 10 to the 4 as an overall limit of detection for the device.

Moving on to the potential strategies to mitigate the residual risk of bacterial contamination of platelets. We have four options to consider and discuss. Option A consists of shortening of the platelet shelf life to four days. The rationale is as follows. As I mentioned earlier, platelet storage at room temperature can result in the proliferation of bacteria. It has additionally been shown that the percent of contaminated units directly correlates with the length of platelet storage. The cumulative data from different sources show that septic transfusion reactions and related fatalities are associated with transfusion of all of the platelets.

This is the American Red Cross data on the distribution of septic transfusion reactions and fatalities

by the transfusion. On these slides, there are two sets of data. The first one is covering the period from 2004-2006. At that time, the Red Cross was sampling 4 ml into the bacterial bottle, and 39 percent of their collections used diversions. During that period, 1.5 million components were distributed and they were associated with 20 septic transfusion reactions leading to three fatalities.

If you look at the distribution by day of transfusion, the lion's share was on day five, 65 percent of septic transfusion reactions and 100 percent of the fatalities. Day four had 20 percent of the septic transfusion reactions, day three 10 percent, and day two 5 percent.

This first set of data is published. The second set of data, 2007 to 2011, is unpublished and was kindly provided to us by Dr. Richard Benjamin from the Red Cross, who will have his comments on the data later on in his presentation.

The second period, the sampling was 8 ml using 100 percent diversion. Four million components were distributed during that period, with 38 septic transfusion reactions leading to four fatalities. The distribution, this time for day five, you had 53 percent of the septic transfusion reactions on that day, and 50 percent of the fatalities. On day four, you had 42 percent of the septic

transfusion reactions and 50 percent of the fatalities. Each of day two and day three had 2.5 percent of the septic transfusion reaction. In the second periods, there a shift away from the peak at day five.

This is from the Canadian discovery, which I describe earlier. If you look only at the apheresis product, they had two septic transfusion reactions, including one fatalities, both occurring on day five. If you combine apheresis and pooled, they had five septic transfusion reactions, four occurring on day five, including the fatality, and one on day three.

The Jacobs PGD study, they had two of the 12 confirmed positive were transfused and led to a septic transfusion reaction, and both were the five platelets. The PASSPORT study had three confirmed septic transfusion reactions, two were on day four and one on day six. In Germany, 80 percent of the fatalities were from day five platelets.

Shortening of the shelf life to four days, we believe, will decrease septic transfusion reactions and related fatalities, and will also decrease the maximum bacterial load at the end of storage. Four day platelets would still be tested by early culture to intercept the fast-growing organisms. Germany recently shortened the platelet shelf life from five to four days, to reduce the

incidence of sepsis associated with five-day platelet transfusions.

The mantra that is heard in meetings and that is also written about in articles is that fresher platelets is safer platelets. Obviously, this option would elicit major concern over its impact on the blood system and on the platelet availability. There are issues of practicality and visibility, what is achievable.

The data on the distribution platelet transfusion by platelet age are limited, in order to determine what would be the impact on the platelet supply. We went to the National Blood Collection and Utilization Survey, that the 2009 report obtained on data from 2008. The mean platelet age at transfusion, they don't have the distribution by age of transfusion, but they have the mean platelet age, for pools, it was 2.9 days. However, this was based only on 8 percent response from hospitals. For apheresis, it was 3.1 days, based on 53 percent response from hospitals.

Now, the literature has some data on the distribution of transfusions by age of platelets. The Jacobs study, as I mentioned, they tested platelets on the day of transfusion with their rapid test. The percentages here, they represent the distribution of testing. However, it can give you an overall idea about the platelets transfused on those days.

The second study, Welsby, this was a study to determine whether there's any association between outcome after cardiac surgery and the age of the transfused platelets. These were the percentages of their transfused platelets. The third study, the Kleinman study, this was in fact the investigators of the PASSPORT study. They conducted an analysis about the impact of the discontinuation of the seven-day platelets. While they did not have raw data on file, but they estimated that 20 to 30 percent of platelets are transfused on day five.

Not all the data is appearing in the slide, but this slide is from America's Blood Centers. It was kindly provided to us by Dr. Lou Katz. This is data obtained from about 3500 apheresis platelets transfused from three centers. It showed that the percent of units transfused on day five was 44 percent. Those transfused on day four, 41 percent, day three, 12 percent, and day two, 3 percent. Dr. Kats said this reflects his experience of the hospitals he worked in.

That was option A. Option B consists of retesting with the rapid test, after a four-day storage. This is predicated on a shortened shelf life to four days. This option consists of free testing platelets, meaning after an early culture with a rapid test, after expiration at day four. After day four, and up to day seven, the

platelets may be transfused, if found negative by a rapid test conducted with four hours prior to transfusion.

The four hour timeframe was set to define a period of relative safety, following a negative read by a rapid test. It is based on allowing no more than two bacterial doublings, following a negative read by a rapid test. This timeframe would be consistent with the current time limit on transfusing poor storage for platelets as a control on bacterial perforation.

Option C consists of retesting with a culture on day four with extension to day seven. This is again predicated on a shortened shelf life to day four. As I mentioned earlier, the residual risk of bacterial contamination on the day of transfusion with an outdate is estimated to range between 1 in 1000 to 1 in 2300. Therefore, a culture on day four would detect and interdict a number of bacterially-contaminated platelets from being transfused. It would decrease the residual risk of bacterial contamination late in platelet storage, and could potentially permit the extension of platelet shelf life to seven days.

A similar concept has been implemented by the Irish Blood Transfusion Service, where about 193,000 platelets combined apheresis and pools were transfused with no transfusion associated septic reactions observed under a

comprehensive active haemovigilance system. This is the data from the Irish Blood Transfusion Service. It is based on the published paper from 2008, with updates from Dr. Murphy.

As I mentioned earlier, the Irish Study tested apheresis and pools on day one, four and at outdate. They used both aerobic and anaerobic bottles, 7.5 to 10 ml from each product. The rate on the one was about 1 in 3000, so there were 14 confirmed positives, eight in pools, all gram positives and six in apheresis. Two of them were gram negatives.

The day four contamination rate was 1 in 3300. It was one case in apheresis, a gram positive. At outdate, the rate was in 1 in 1100. You had two apheresis and five in pools, and all gram positives. This is the cumulative data from the Irish study, strictly on apheresis platelets. The day one confirmed positive was about 1 in 3000 units. There were a total of 19 true positives and apheresis.

In the earlier study, there were six, and so total, they had 13 additional, and they were all gram positives. The day four confirmed positive, so they had found that only one contamination. This time, the denominator is about 33,000. The outdate, so day six or day eight, the rate was in 1 in 2700. Again, the same gram positive I showed you earlier. Despite that there was some

confirmed positive outdate, there were no reactions observed over the period that this strategy has been applied in the Irish study.

This option would apply to platelets stored in containers cleared for seven days, using an aerobic bottle on day one, and then aerobic and anaerobic bottles on day four, using an eight to ten amount of volume per bottle to increase the yield on the four. Post-marketing surveillance study would determine the effectiveness of the introduced measures in decreasing the rate of contamination.

Option D, so this is the last option, this consists of culturing platelets using the concept of a constant proportion sampling volume. Currently, the sampling volume is fixed, regardless of the volume of the platelet collection. This concept consists of sampling a constant proportion of all platelet collection. The objective is to increase the sensitivity of the culture, by decreasing the sampling error.

The bacterial content and sampling time has been determined to be ranging from 5 to 60 cfu per platelet product. The detection of contamination in platelets is considered a rare event, and can be modeled by the Poisson distribution as it is illustrated in this graph. On the Y

axis, you have the percent of detection, and on the X axis, you have the bacterial load in the container.

The lower graph represents the percent detection using the current 8 ml volume, and the upper curve represents the detection by using a constant proportionate sampling volume. The proposed proportion was 3.8. For example, at 30 cfu per bag, the detection would increase from 41 percent to 68 percent. At 5 cfu per bag, the detection would increase from 9 to 17 percent.

The advantages of this option, studies have shown that with increased sampling volume, you have a trend towards an increase in the detection rate. You also have a decrease in the indeterminate results, so these are the initial positives that were not confirmed because the product had already been transfused. It also leads to a decrease in time to detection, leading to a decrease in the whole period between sampling and product release. That facilitates the inventory management.

The disadvantages of option D is that it is a theoretical model with a number of assumptions. The increase in detection depends on the actual bacterial concentration in the product, so the increase is not uniform between the two curves. A number of studies have shown that an increase in sampling volume leads to an increase in the false positive rates. Again, you would

have a concern over the discard of suitable products. Compliance issues may arise, related to the complexity of the testing strategy, because you no longer are sampling a fixed volume. This option D, this would be an adjunct option to be used with options A through C.

Moving on to the questions to the committee, question number one, does the committee find that additional measures are necessary to decrease the current risk of transfusion of bacterially contaminated platelet products? If yes to question one, please discuss whether a reduction in platelet products shelf life from five to four days with early culture, would decrease the risk of transfusion associated septic reactions sufficiently to obviate the need for additional testing.

Whether the available data are sufficient to support an extension of platelet shelf life up to seven days, if otherwise expired four-day platelets with negative day one cultures are retested with an FDA-cleared rapid test, and released within four hours of a negative test result.

Whether the available data are sufficient to support extension of platelet shelf life up to seven days, if otherwise expired four-day platelets with negative day one cultures, retested on day four with an FDA-cleared aerobic and anaerobic bottles culture-based method using 10

ml per bottle. Whether for options A, B and/or C, the bacterial cultures should be conducted using a proportionate sampling volume, and whether there are other tests-based options that FDA should consider.

Question three, please discuss whether alternatively for platelets limited to five days of storage, the available data support a strategy to culture platelets after the first 24 hours of storage. Then, retest just once with a rapid test on the day of transfusion.

Question four, please discuss the role of surveillance for any of the options listed above in determining the effectiveness of any new strategies implemented by blood collectors or transfusion services, such as culture testing of the platelets product at the time of transfusion or at product outdate, to determine the residual contamination rate and/or active monitoring of septic transfusion reactions. That concludes my talk, and thank you for your attention.

DR. HOLLINGER: Thank you, Dr. Haddad. It was very concise and we appreciate it. We will move on then to the next speaker, Michael Jacobs, from Case Western Reserve University, who will talk to us about microbiology platelets of platelets for transfusion.

Agenda Item: Microbiology of Platelets for Transfusion, Michael Jacobs, M.D., Ph.D., Case Western Reserve University

DR. JACOBS: Thank you, Mr. Chairman, Dr. Epstein, ladies and gentlemen. I am very honored to be asked to give this presentation, and I feel particularly honored because there are so many people in this audience who have had a lot of experience with this, with millions of units of platelets being given in some instances. I am going to try and give you an overview.

Also, many of the points that I have to make were made by Dr. Haddad, so I am going to go over them very quickly. Also, for disclosure, here are my disclosures and they have been made available, as well.

Now, bacterial contamination of platelet products, again, you have had an overview. The questions I am going to address are what is the prevalence of bacterial contamination of various platelet products? What bacterial species are found? What are the effects on patients of transfusing these products? This is a key issue, what has been done today to decrease the risk? You have heard a lot of data on this already. How effective have these measures been, and what additional steps can be taken, is what we are discussing today.

Just for comparison, this is a figure put together by Dr. Brecher, who is in the audience, on the relative risk of viruses that has gone down considerably. This is only showing up to 2001, but showing big increases in viral testing, whereas bacterial contamination of platelets has remained relatively constant, although, we have had some improvements since 2001.

Just to set the scene, also over 3 million platelet units are transfused in the form of about 1.8 million apheresis units and about a quarter of a million pools. This is an important distinction. These are produced in two ways, some of which are pooled at production, some of which are pooled at issue. The ones pooled at issue, some are leuko-reduced at production and some are leuko-reduced at issue, and this makes a difference.

Bacterial contamination rates are similar for apheresis and whole blood-derived units, with contamination rates four to six fold higher for pools. It is estimated that over 500 bacterially contaminated apheresis units and a similar number of random units are transfused each in the U.S. As you heard, fatality rate is about two deaths per million units, or about six deaths per year. The rate of septic reactions is 10 to the 13 per million, or 30 or 40 cases per year.

Now, just to go back on some history, Dr. Buchholz, who was a pioneer in the use of platelets many years ago, in 1971, studied platelets and found that 1.4 percent of his platelet supply had greater than 1000 organisms per ml. I want to emphasize quantitation, the number of organisms per ml of platelets is key to understanding this whole issue, and what the risks are at different times, and how you detect them.

Fast forward 20 years, I became aware of this and I would like to acknowledge Dr. Rosalyn Yomtovian as also in the audience, who introduced me to this topic when she walked into the microbiology lab, and the director of microbiology with this tube of platelets, and saying, Houston, we have a problem. Not only did we have a problem, but very shortly afterwards, we had four problems.

We were very concerned about this and Dr. Yomtovian very appropriately investigated this very thoroughly. What we found actually that this was just random clustering of rare events, and that our contamination rates are no different. It did stimulate us to culture most of our platelet units from that time onwards, and we are still doing that to this day. We have generated a lot of data during that.

Fast forward 20 years past that, though, to some extent, it has been very frustrating because, as you can

see, we still continue to get bacterially contaminated platelets, about four a year. The only time we didn't see any was as Dr. Haddad had mentioned, when you don't look for them, you don't see them. Passive surveillance, you only pick up a fraction of your contaminated units. We stopped doing surveillance in 2000. We restarted when early culture was introduced to see how effective that was. As you can see, we are still seeing contaminated platelets.

Now, what are the organisms involved? The predominant organisms I have shown, FDA fatalities, which are the most important ones, and I have shown overall. One limitation on our overall data from Cleveland is we have only cultured aerobically, but I will mention anaerobes which are relatively unimportant in bacterial contamination of platelets.

As you can see, the majority of organisms, both overall and in fatalities, are staphylococcus, both staph aureus, but also CoAg neg staphylococcus, the majority of which are staphylococcus epidermidis. We some bacillus, gram negatives have gone down a lot, and on occasion, other organisms are seen. In this series, there was only one anaerobe involved, as far as fatalities were concerned.

You have seen this slide before, just again to make the point that the odds ratio of picking up bacterial contamination by active surveillance is 32 fold higher,

sepsis is 16 fold higher. Death, when they are caused by bacterial contamination, are generally recognized. Not always, because they are not always immediate.

Now, what is the age of platelets? This is a critical issue and you can see here in our series, this is our series of data going back to 1991 to 2004. You can see that we had an equal number of any profusion reaction 10 at day five, versus 10 at less than day five, no statistically significant difference. As far as severe reactions, we had more on less day than day five, three versus three at day five. Again, this was not statistically significant.

As far as apheresis units, Dr. Benjamin is going to be giving a presentation on this, and Dr. Haddad has also shown you a summary of this. The conclusion or the point about this data, is that changing the outdate to four days would certainly decrease, but would not eliminate septic and fatal reactions.

Now, one of the things I have tried to do during my presentation is try and make different studies comparable, by showing them in this format, rather than showing them as percents, or 1 in 1000 or what the rate is, by looking at the rate per million. This is bacterial contamination per million units, in this case, apheresis units. It shows the value and the 95 percent confidence intervals.

I have tried to show all of the data that I am going to discuss in the same format. When the 95 percent confidence interval wasn't shown in the initial publication, I have calculated that and added this. This shows our data on apheresis units, starting off in 1991 and up to 1999, we had a contamination rate of almost 400 per million units, 5 out of 12,000. This represents about 50,000 apheresis units.

We didn't do testing 2000 to 2003. We restarted 2004 after early culture was introduced. We found our rate was not statistically significantly different, but it had gone up slightly. Diversion and skin prep, again, there is a slight decrease, but again, you can see the 95 percent overlap considerably on all of these. The point from an end user, as they use our platelets in our institution, we are still finding contaminated platelets, and you can see at the rate of about 1 in 2000.

When we look at random donor pools, you can see we did see a big difference in 2007. The reason for this is we changed from pooling at issue to using pre-pooled platelets provided by our provider. One important point about all of the whole blood-derived platelets that we use, they are all leuko-reduced at production, going back even to before 1991. Units leuko-reduced at production were tested in the study.

There is some evidence, and I think this is the reason why the detection rate in whole blood-derived units, leuko-reduced just before use, is much lower, because I think the leukocytes are killing the bacteria. Unfortunately, in the study that Dr. Haddad mentioned, no cultures were done to tell whether the low detection rate was because the test didn't work or because the contamination rate was really low. The other point here is that when you do pre-pool, you get a big improvement in safety.

Again, you have seen this data in different format, that early culture of apheresis units appear to be effective at intercepting most gram negative contaminants, but does not effectively address gram positive contaminants. Now, one of the points I have made earlier is the number of bacteria that are contaminating the unit are absolutely crucial. This is an important point about the age of platelets. One of the big differences between bacterial contamination and any other infection that is being transmitted is that bacteria are not static. They are capable of growing.

We put this data together. It took us a long time to do this. We have had 65 patients unfortunately who received contaminated platelets. The one thing that I did right from the beginning, and I can't give you a good

reason as to why I decided to do this, but when Dr. Yomtovian walked into the lab and said, Houston, we have a problem, I said, as a microbiologist, I can tell you if there is old bacteria in there and I can tell you how many there are. That is as far as I can take you, but that has taken us a very long way.

You can see here what this has shown us, and this is the only information I am aware of that has looked at this, and certainly in live patients receiving products, is that if you have fewer than 10 to the 5 organisms per ml, you either don't get a transfusion reaction or you get a very mild reaction. Greater than 10 to the 5, you have a variety of reactions. Ten to the 5 is a critical clinical breakpoint. It is not absolute, but you can see here, there is a pretty good correlation.

The other thing we found was that reactions are based on organisms virulence, more likely 3.5 fold to get any reaction for more virulence species, staph aureus, gram negatives, bacillus. Almost nine fold more likely to get a severe reaction with a virulent organism.

As far as bacterial load, again, any reaction 4 fold higher for a bacterial load greater than 10 to the 5, and for severe reaction, greater than 34 fold. Conversely, we found, but with a limitation, that this a limited series, that we didn't find any difference based on patient

age. You have seen several data series showing this, that you get severe reactions at day five and before day five.

Earlier detection, how effective is culture of apheresis collections of 24 hours or roundabout there, being in detecting bacterial contamination. Again, you have seen a lot of this data, but I am just showing you this in a common format. This is Dr. Murphy's study, and he is going to give you an update on this. Regard this as preliminary, because he has got much more data now. You can see here, he found no difference in contamination rate between apheresis and pre-pooled, whole blood-derived, very similarly to what we found with anerobes(?).

He found some contamination. We looked at platelets on day four, and he has got an update on this. We looked at outdate. He was getting about 800 per million contaminated units, when we looked at confirmed positives. All positives are difficult to interpret, because you don't know how many of those were real, because many of them were not confirmed. I am showing them in both formats.

Also, an important point is that anaerobes occasionally will cause bacterial contamination. Most anaerobes cannot grow in the air of eclatla(?) bag. Occasionally, clostridium perfringens will grow. There have been three or four cases that have been described in the entire world literature, so this certainly is the case.

The most common anaerobes seen, which is propionibacterium acnes is essentially a non-player. In the U.S., it has not been described as causing as severe or fatal reaction. There are some cases described from Europe.

One of the things I have also done in some of these series is exclude anaerobes. Either way you cut it, there is not much variation that early detection detects about 30 percent of contaminants, based on cumulative issue, if day four culture picks up approximately 60 percent.

Another study that Dr. Haddad referred to was the Pearce study. Again, here the overall detection was 40 percent. If you exclude anaerobes, this comes down to 22 percent. Early detection, this shows some comparisons of data. Red Cross has a lot of data. One of their earlier publications showed 166 per million, and there were an additional 526 per million false negatives or indeterminates. You can see here the rates in the European studies were slightly higher, but the 95 percent confidence intervals all overlap considerably.

Now, the critical issue is early detection is certainly helpful, but what is getting through from not being detected by early culture. You can see here it is approximately double the rate of what is being picked up by early culture. You can see in the PASSPORT study, I have

shown this two ways because they show it 4 out of 6000 had bacterial at issue. Two of them were confirmed and two of them were unconfirmed. If you use only confirmed, that brings the rate down to 330.

Murphy's data at outdate, from his publication, was 483 per million. Pearce's study was about 900, again excluding anaerobes. By plate culture, we were finding about 500 per million. You can see all of these are showing pretty much the same, if number of units that are contaminated at issue.

An important point is how does this compare to production versus issue. You can see here, generally the detection rate is round about 25 to 30 percent. The Pearce study was 40 percent, but you exclude anaerobes, that goes down to 22 percent. The bottom line is, as I think there is no question about it, early culture is effective to some extent. It is very effective on picking up the false gram negatives. Overall sensitivity is low.

You can understand this if you look at generation times of organisms. I am showing here that you can see the detection limit is roughly one organism per ml, when you culture at 24 hours, using an 8 ml volume. When you have a slow grade organism, you can see here at the 24 hour time point, your probability of picking this up is extremely

low. This is an organism that is really growing slowly a generation time of eight hours.

If this increases to four hours, you will still not pick it up in 24 hours. You may or may not, if you are right at that detection limit. If it grows with a one hour generation time, then you are very likely to pick it up. You can see here there is considerable variation in generation times. Most bacterial of the contaminant platelets grow at room temperature, between one and four hour generation times. The average is approximately two hours. Between the purple and the green lines is where most bacteria are going to grow, once they get into lag aerobic phase.

The kicker in this is that many organisms will not immediately go into lag aerobic phase. Here in this example, you can see the organism started growing, but then the antibacterial properties of the platelet unit killed it. The unit itself sterilized. This explains why some of the initial positive cultures are not confirmed when you go back, because after the additional storage period, the bag has self-sterilized.

Conversely, some of the organisms don’t go into lag phase straightaway, and this is probably fairly frequent. Then, when they do go into lag phase, this can be several days later. It is going to depend on the growth

rate of the organism. Again, for all of these reasons, early culture, that 24-hour time point, is going to, by definition, based on the contamination rates or the number of bacteria per bag, is going to, by necessity, be low.

What additional steps can we do to further reduce the risk? We can pre-pool and culture whole blood-derived platelets to bring their level of testing up to that of apheresis units. Also, leuko-reduction at near time of use, versus production, also may be useful. This needs to be proven because cultures have not been done on that subset. This does not address the residual risk in these or apheresis units.

We can optimize culture volume and conditions to improve sensitivity of all early culture. Gains will be limited, due to sample timing and volume issues. We can improve monitoring of patients receiving patients and awareness of septic reactions, because this is important to improve detection of cases, to allow interdiction of co-components, which are frequently, especially split apheresis units contaminated, as well.

The final thing on this list is we can test on the day of transfusion with a rapid test, and the question is, what is its clinical efficacy? Finally, which is not under consideration, pathogen inactivation, currently not

available, and its safety, efficacy and cost-effectiveness need to be determined.

This shows data from the Red Cross, showing that diversion and pre-pooling have been effective. Limitations of culture, because of issue I have discussed, too few targets to reliably capture an organism, and the probability of organisms based on the volume use sample. You have to get a very large volume to pick up various numbers of organisms.

I am not going to spend a lot of time on this. Dr. Haddad has covered this extensively. Using different volumes, you can tweak the system to make some improvements. Sepsis rates were higher based on the size of collection, but similar based on distributed units, based on data from the American Red Cross.

Now, this leads me to how can you detect these on day of issue. This was a study that I was also very fortunate to be involved in, detection of bacterial contamination of culture negative apheresis platelets on day of issue, with a PGD test. This was a study you have seen a lot of the data of, so I am going to go through this fairly quickly. The statistical design was that, based on this limit of 10 to the 5 cfu per ml being clinically significant, and based on that being the sensitivity of the

test, that we should be able to pick up about 438 cases per million, roughly 1 in 2200.

We also did a concurrent culture. Unfortunately, we could only get this done on about a third of the units. I would have liked to have done them on all. The test, as you have seen, detects bacterial cell wall antigens, sensitivity for most organisms is in the 10 to the 4 range. There were a few that are higher than this.

We used the usual definitions and reactive was defined as repeatedly reactive as is typically done. There were 151 repeated reactive, of which 142 were culture negative and nine culture positive. To make one point, when you are looking for a very rare event, 1 in 2000, 1 in 3000, even very low rates of false positives, you are going to get way more false positives than you are going to get true positives. There certainly is room for improvement, and virtually all tests that have been introduced, improvements come along as second and third generation tests are developed.

The important part of this also is that 10,000 of these units were cultured, and you can see here, only two that were negative by the PGD test were culture positive. I am going to give you the information on all 12 positives that we had.

The true positive results were as expected positive organisms, two bacillus species, one enterococcus and the rest of CoAg negative staphylococcus, one enterococcus. Two of these were transfused, and one caused no transfusion reaction and one caused severe septic shock in a CoAg negative staphylococcus. The level of contamination of these three that were true positives were 10 to the 6, to 6 to the 7, so about one to two logs above the higher limit of detection of the test.

As far as age, you have seen this data, as well. Four of them were on day three, two of them on day four, and three of them on day five. Six of nine positives were in units that were less than five days old. Now, the two false negatives, one was a CoAg negative staph at 100 organisms per ml. This is two logs below the limit of detection of the test, so I disagree with Dr. Haddad's classification. You can't include this as a false negative. The test wasn't expected to pick this up.

The streptococcus aureus was a 10 to the 7. It was very high. What this turned out to be was a very rare example of a viridian strep. There are two main groups of viridian streps, and this organism had not previously been described as a platelet contaminant. The antibody to viridian streps that was present in the reagent covered the

other viridian streps. The company is now adding antibodies to cover this one, as well.

Then, in addition to this one case was picked up by passive surveillance. This was a five-day unit, streptococcus sanguinis was grown. Unfortunately, a culture wasn't done, but the gram stain was initially negative, when the culture was positive, went and looked at it again. They did manage to see a few organisms, which tells me that the organism load was in the 10 to the 4, 10 to the 5 range, which is the detection limit of gram stain. This turned out not to be a septic transfusion reaction. The patient had an allergic non-febrile reaction.

One of the issues and the big concerns about the study is, despite its success, was addressing false positives. Ways of addressing this are firstly to look at the rule of three, to do a retest and make sure you have got a reproducible positive. Then, if you do have a positive and you do want to use the unit, you can do further testing on it.

There are a number of ways you could do it. For example, gram stain or acridine orange on a concentrated cytospin specimen would bring the detection level down to about 10 to the 4 organisms per ml, and would take about an hour to perform. You could also culture, but then you would have to wait 24 hours for that result.

You would also transfuse slowly with antibiotic coverage, if there were no other units available or the unit was HLA-matched. Improvements are in development, including simplified test procedure, improved sensitivity using larger gold particles, improved range of bacteria detected, and reducing the false positive rate.

My conclusion from this study, and I put this out as a challenge because as far as I can see, on a scientific perspective, this is the most successful detection and interdiction study of bacterially contaminated apheresis platelet doses reported. Certainly, as far as the U.S. supply is concerned.

I hope this record won't stand and that we will have better tests, but at the moment, this is where we stand. That detection rate, if you remember, we were expecting to find around about 400. We found 326 contaminated units per million. Based on this rate, this would detect approximately 550 contaminated units per year in the current U.S. apheresis platelet supply. This would prevent over 300 significant transfusion reactions and several fatalities per year.

This illustrates on the graph of reactions, the level of organisms that you would detect by this test, and the transfusion reactions you would prevent. Based on our series, it would be about 55 percent of units with a

greater than 10 to the 5 of gram positive species resulting in transfusion reactions.

The conclusions, as published in the Journal of Transfusion, was the test detected bacterial contamination in 1 in 3000 units. It released as negative by pre-storage culture in platelets as young as three days old. Three contaminated doses, two clinically insignificant, had nonreactive tests, while .51 percent of tests were false positives.

Application of this test on day of issue can interdict contaminated units and prevent transfusion reactions. To make this point, this study studied approximately the number of platelet units that is used every week in the U.S.

Again, to put this in perspective, we were expecting around about 400. You can see the confidence interval of this test compares very favorably with culture-based methods, and is the only one of these methods where the result is available before the unit is actually transfused.

For about seven years, we gram stained all of our apheresis units. We had three contaminated ones. We didn’t pick up any of these by gram stain, out of 8000. Whereas, out of 27,000, we picked up nine, using the PGD test, during the multi-center study. Again, putting this

in perspective of the early culture results that I have shown you, where results are not available prior to transfusion, and in comparison to the Murphy data, you can see here this success rate, and this is the reason I am making the claim that this was the most successful study ever done, in a method that can pick them up before the unit is transfused.

I am showing 75 percent, based on the cultured subset. The numbers are small, three out of four were picked up. Of the non-cultured set, we are only aware of one. It would have been nice to have cultures on the rest, but I think that you can see that the contamination rate, based on the overall contamination rate, indicates that we did pick up the vast majority of contaminated units.

Now, to get into testing requirements, there is an AABB interim standard. The service shall provide methods to limit and detect or inactivate bacteria in all platelet components. Furthermore, detection methods shall either be approved by the FDA or validated to prove sensitivity equivalent to FDA approved methods. I have no idea what that statement means. Are you referring to an FDA approved method that has 20 percent sensitivity or 80 percent sensitivity? How do you do this? There is no specification.

FDA approved methods include BacT/ALERT, eBDS, PGD test and BacTx. But there is no guidance provided on when or how to use these tests, and none are approved as release tests, and therefore, none of them are really required to be done. This is what I am hoping the committee will address today. This statement is the most important statement of what I have to say.

In conclusion, what is the prevalence of bacterial contamination? Current U.S. platelet supply, about 600 in apheresis units, about 400 in pools. What bacterial species are found? Predominantly staphylococci and streptococci, but the few gram negatives, when they do occur, are highly virulent.

What is the effect on patients of transfusing these products? Sepsis, which can be fatal in over 50 percent of patients contaminated with bacteria containing greater than 10 to the 5 organisms per ml. What has been done to date? Diversion, skin prep, early culture, pre-pooling, testing at-issue, all of these have had various efficacy, as you have seen.

How effective have these measures been? Prevalence in apheresis units has decreased by about a third, with skin prep and early culture. What additional steps can be taken? Shorten outdate, that is totally impractical. Currently, about 8 percent of the entire

platelet inventory outdates because the outdate is too short. You reduce that to four days, that number is going to skyrocket even more. About 20 to 30 percent of platelets are used outdate five at the moment.

Pathogen reduction is not yet available. Retest by culture midway during storage, that is impractical, unless you have very tight circumstances where the collecting center can do the additional testing. It is totally impractical to be done at the hospital level. Use at-issue, I challenge you by stating that this has been proven by the PGD study.

In conclusion, I would like to thank you for attention. I hope that you have had more attention than this audience member did and that many of you have stayed. Thank you.

DR. HOLLINGER: Thank you, Dr. Jacobs. The next speaker, William Murphy, from the Blood Transfusion Clinical Programs in Ireland, will speak to us about the experience of the Irish blood transfusion service.

Agenda Item: Experience of the Irish Blood Transfusion Service, William Murphy, M.D., Blood Transfusion Clinical Programmes, Ireland

DR. MURPHY: Good morning, everybody. I would like to thank the organizers for inviting me. It is a

great privilege to be able to participate at this meeting, and to share our experience with you.

Basically, this is what we do. I will describe why we do it, possibly how we do it, and what we have discovered from doing it, and what we are planning to do next. Since 2004, we have done a day one test, or day two, using 100 percent testing. We started off with the 1 x 8 ml sample. It took me a while to remember why we changed to a two-bottle sample in 2005. The reason for that was that at that stage, the Welsh blood transfusion service were doing a two-bottle, and they reported to us that they were seeing a number, in fact most of their positives were seen in only one of two bottles. We moved to a two-bottle sample at that stage. That is why we moved from 8 ml to 15 ml.

We do use an aerobic and an anaerobic, but actually, it doesn't really matter that we use an anaerobic. We got a lot of P acnes as a consequence, but anaerobic bottle will grow aerobes quite well, as well. If we hadn't moved to an aerobic and an aerobic, we would have moved to two aerobic. That is the second bottle, which we think is very important, or the size of the sample, which we think is important, is more important than whether we use an aerobic sample or not.

In 2005, and I will explain how we did this in a few minutes, we extended the shelf life to day seven if we got a day four retest that was clear. We thought, in line with a lot or some of the European blood services, that we could extend to day seven storage of platelets on the basis of the day one test. The Dutch do that and they have done that for a long time, and they don't have a serious problem with it.

We went to our regulator and asked them if we could do that, and they said no. It is such a small word and it comes so easily off of the tongue. But they were right, so I have to acknowledge their participation in this.

At that time, and up to about 2008, we also tested all expired platelets that were left in-house. There is an important logistic point here, which does not necessarily apply elsewhere, and that is we tend to store all of the platelets in the blood service. Ireland is a small country with terrible roads. We do tend to hold all of our platelets in-house, and then the hospitals draw them down on demand. Most of the big hospitals are close to a blood center. There are an awful lot of small hospitals that are not close to blood centers, but they use fewer and fewer platelets.

We tend to hold the platelets in-house. We have got them all, unless they go out and are used on the day of distribution. That is actually quite an important point. It means that it is easier for us to do a day four retest. I don't think it is impossible for us to do one that has been distributed already. It also means that all of the platelets that expire, expire in-house, we have them. That is why we have got those data. We don't do expired testing anymore because we have run out of money, or rather, the Germans have run out of money, so we don't have any money.

We actually started to do bacterial testing of platelets because of TRALI. I will explain that, as that is a bit of an Irish statement. Nevertheless, it is true. Basically, we were mindful of what had happened around Yersinia enterocolitica. I came to Ireland at the end of 1996. Before that, I had worked in Edinburgh for a number of years.

I think it was 1991, we had two fatalities a couple of months apart of Yersinia enterocolitica in red cells. We had never seen them before and we have never seen them since. We published a number of studies around that. We did a fair amount of culture studies around that. What I learned was that blood collection processing and storage provides really a unique microbiological niche. The growth of bacteria, the ingress and the growth and the

subsequent clinical disease associated with bacteria is actually dependent very much on the conditions of that niche.

By taking bacteria, which you would normally clear from your blood system, Yersinia enterocolitica, which would be present in your blood during the bacteremia, which is not necessarily a septicemia and generally is not, you then store that blood at 4 degrees. It kills the immune system, or turns off the immune system. That would clear those in your blood. We don't all die every time we get gastroenteritis from Yersinia eterocolitica, very few of us do.

If you take the blood during the bacterimic phase, turn off the immune system, but allow this bacterium which grows reasonably well at 4 degrees, to proliferate, you then turn what would be quite a benign bacteremia into a fatal septicemia when you then transfuse that unit. Even if you transfuse it back to the person who gave it to you, and there have been at least one, I think two, cases of fatal transfusion reactions from Yersinia. People who had Yersinia bacteremia at the time of donation, they cleared the bug from their blood, but it grows quite nicely in the blood packet 4 degrees. When you give that back to them, it turns out their lights.

There is also the issue that actually Yersinia, as far as I know to this day, has only been described in either red cell concentrates or more specifically in solution of red cell concentrates. It has been around forever. It didn't appear until we started making red cell concentrates in the late '70s and '80s. Then, it has more or less disappeared since leuko-depletion came in.

Some of the studies we did in Edinburgh suggested that, in fact, the rate of cooling and also the relative concentration of plasma is important in allowing Yersinia to grow. That is just speculation or conjecture. What we came away with from that was that you have to be careful when you change the milieu in which you are preparing platelets or blood components.

You are going to get bacteria into platelets all the time. If you culture straightaway after collection, at least 1 in 100 as the Dutch have shown, have bacteria in them. Almost all of those, as Dr. Jacobs showed, will die away. They just do not grow in blood, which is why we survive as a species, but some will survive. If you change the conditions, then you may well change the epidemiology of your bacteria.

We were very loathe to introduce platelet additive solution to try and reduce the incidence of TRALI, which was a problem, without a bacterial test for our

platelets, because we were changing the ecology of the platelets. My experience with Yersinia was that if you actually dilute out the plasma, that you may well see additional growth of bacteria and an additional problem from bacterial growth in platelets, or bacterial contamination in platelets, which is certainly there.

To get around the TRALI issue, we introduced the bacterial testing, so we could introduce additive solution for platelets, and that is what we did. It is important to remember that if and when we move to additive solutions for platelet storage, for platelet apheresis storage, which we probably will, then all of the data that we have generated to date will need to be revalidated. I am not saying they are false, but they will need to be revalidated because the rate of growth will change, a good deal for some bacteria. You will have to go back and, presumably in the phase four mode, relook at those data again.

We also discovered that, within each species, the growth characteristics in Yersinia, within isolates of Yersinia, we collected some from around the place that had given septic reactions in other transfusion services. They differed. There was no such thing as an exemplar of a species. Each strain has different characteristics.

The rationale for day four, retesting on top of that, was because we wanted to extend, to get value for our

test. We wanted to extend to day seven, and our regulator said no, as I said. We thought, well, bacterial testing before issue of day five platelets improved safety. That is a reasonably uncontentious statement, but it may not be true. It may, in fact, decrease safety because it might push out the number of transfusions around day five, rather than day one or two or three. Because you're testing and holding, you now transfuse later in the platelet lifespan.

I don't know you feel about the data for the evidence of seatbelts. There is no doubt that seatbelts have increased the fatalities of pedestrians and cyclists. What about parachutes? There is no doubt that the invention of parachutes has cost hundreds, if not thousands, of lives from people jumping out of airplanes. If there hadn't been a parachute, they wouldn't have jumped in the first place. You can't take it as proven that actually testing for day five improves safety, because we know the test that we have are not 100 percent sensitive. It certainly doesn't mean that you can extend the shelf life to day seven, on the basis of day five.

We had to look at what happens to platelets. These are apheresis, buffy coated derived pools. We looked at what the manufacturing process did to the level of contamination. We published this in Transfusion in 2000. We collected 19 different clinical isolates of CNS, so

these weren't from a catalog. We actually got these from the labs. Most of them had been discovered growing in platelets or whole blood donations from blood donors.

We spiked these into whole blood collected shortly beforehand. We then sampled all of the way through the manufacturing process, to see what happened, what was the natural history of contaminating staphylococci in the blood product. What we found is that the detectable contamination, using bacterial culture, fell. We inoculated, we immediately tested to see if there bacteria there. We recovered bacteria in 15 out of 19 cases.

By the time we were finished processing, which included leuko-depletion at the end of an overnight storage of the blood unit, then extraction of the buffy coats, pooling of the buffy coats and making of the platelets, that we were down to 1 to 10 cfu. We were down to undetectable levels in most of the units. At 1 to 10 cfu per ml, which is low, and similarly at 10 to 100 cfu per ml.

The manufacturing process gets rid of most, but not all, bacteria in this experiment and setting. That really meant that we were starting after manufacturing, with very, very low levels of bacteria. We haven't sterilized the units. The processing, the leuko-depletion,

the overnight hold, reduces the bacteria load, but it doesn't sterilize them.

We then thought that we should apply a similar level of sensitivity or a similar goal of sensitivity through the bacterial test on this product, as we would to a viral test. We wanted a test with 99.5 percent sensitivity to detect a bacteria in the bag that was going to be clinically relevant. We knew there were some data around at that stage that suggested you don't see much in the way of septic reactions below 10 to the 5. We have ourselves an order of magnitude below as a tougher test.

We wanted to test this bacterium that was now growing from the very lowest levels, there has to be at least one bug in the bag for it to grow. It would grow to 10 to the 4 cfu per bag by the end of day seven, so we were trying to convince our regulator to let us hold out until day seven. Growing from 1 to 10,000, which should not result in a septic reaction.

This test could detect 1 cfu per ml. At that stage, we were looking at a 10 ml test, that was our starting hypothesis or proposition. We wanted a test that was able to do that. Now, the BacT/ALERT can do that. The manufacturer stated, and in our hands, in fact, it does. BacT/ALERT is able to detect reasonably, with almost 100 percent reproducibility, about 10 bugs in the bottle.

It is important to note that actually the sensitivity of a test, at this level of contamination, depends on the chance of having a bacterium in the test sample. The bigger the test sample within limits, the more likely you are to detect a bacterium. Yes, the test itself has to be able to detect the bacterium that is introduced in the test sample, but you have to have a bacterium in the sample to start with. That is why we went with the BacT/ALERT system, and that is why we ultimately moved onto the 15 ml.

What we discovered was that such a bacterium needed 92 hours of culture in the bag before sampling, assuming, and Dr. Jacobs has addressed this, that it is a log linear growth, which it often is not. We wanted to detect the bacterium on the blue line, drawing from basically one bacterium in the bag, to about 10,000 on day seven, at the end of day seven at expiry.

Where could we test for that, and the answer is we could test on day four. A 50 ml sample taken on day four of shelf life meets these criteria. It also allows this extra 36 hours of growth before the platelet would have expired at the end of day five. We now reckon that our day five retested unit is probably the safest unit of platelets in the history of man, because it has had this 12 hour and ultimately 36 hour, by the time of expiry, retest.

The beauty of this, as well, is you only apply it to platelets that you want. If you have got an HLA-matched platelet or a CND negative platelet, somebody on the go or a group that is of particular interest, that is the one you can retest. You can let the others expire. You don't have to test everything that you have got. You can choose to extend the shelf life of the platelet that you want.

The problem is, and Dr. Jacobs has covered this already, that actually bacteria may not do that. You may get lag phase growth and then linear growth or exponential growth later on in life. You may not detect that with your test. It will fall below the levels of sensitivity. This is what happened.

We started with a pilot study, where we sequentially tested platelets on day one, test them again at day four, and looked to extend their shelf life. This was validation data. This was not a field trial. Certainly after unit number 163, I think, in this study, did test positive at day seven, having tested negative at day four. Now, in our subsequent data, we have never found a unit that tested positive at outdate, that had tested negative at day four. There weren't that many, but we did it in the field. We found this bacteria that grew on the expiry sample, when it had already tested negative at day one, and again at day four.

We took that staph capitis, different staph capitis than the one that subsequently grew in the field study. We took that staph capitis and reinjected, or re-added it back, to platelet. We spiked it back into platelet units at day one, at both 1 to 10 cfu per ml and 10 to 100 cfu per ml. What this shows is that, in fact, it did grow. We did detect in all six of those re-spikings, but we could not detect it before day four, or in two of the instances before day seven. It grew in all of them, but it grew very slowly.

When we applied our line of less than 10 to the 4 by the end of day seven, if we tested that other one, that sort of one on the extreme left a little bit later, we probably would have failed. As luck would have it, we didn't. We were able to convince our regulator that, in fact, it had passed the test. It had not grown above 10 to the 4 on day seven, having been tested on day four. We decided on the base of that, that we were on the limit of perhaps the criteria of the test, but that it was worthwhile going ahead, which we subsequently did.

Just a quick note on what we do, just because I think these are important. We do take the samples in a Class D cleanroom. That is where we manufacture our platelets. The inoculation is subsequently done by technologists who do nothing else, other than bacteriology.

These are not routine blood-banking staff, blood component manufacturing staff. They are bacteriology technologists. I think that is actually quite important.

The inoculation is done in a microbiological safety cabinet, like what is shown in the picture. Importantly, to get rid of contaminating spores, we do immerse the caps. We immerse the bacteria bottles in a sporocidal agent before inoculation. I think that is quite important, too.

Apheresis, as mentioned earlier, is done a minimum of 14 hour hold, a mean of 17. Pooled platelets, which we produce less and less of, are sampled 12 hours after the end of manufacture, which means it is at least 30 hours since the venipuncture took place.

This is also important, and I think this is an important issue that perhaps it is worthwhile addressing going forward. We think there are three types of positives. There are false positives, where there is a signal in the machine, in the automated machine. There are no bacteria in the bottles. The machine has gone off, given you a reading, and when you go and look in the bottle, there is no bacterium there. That is a false positive, there is no bug.

Then, there is confirmed, which is very easy. There is a bacteria in the bottle and in the sample. When

you look back, you can either find the bacteria still in the bag, if it isn't in the patient, or in another component of that donation, or it is in the recipient. That would do. If you have no bag, and it is in the recipient and it was in your culture of the bag in the first place, that is confirmed.

Then, you come to unconfirmed, which I think you tend to call false positives here. They are probably not false positives, some of them, because some of them, what happens is you take a sample, remember, and you stick it in the bottle, where it cultures. You leave the bacterium in the platelet bag. As often as not, that bacterium will die off if it's a CNS or something else. It will not grow. When you go back to sample that bag again, it is not there, but it was there the first time. We call those unconfirmed, and I think they are a very useful thing to measure. They are probably closer to confirmed or true positives, than they are to false positives.

We have seen these data from a couple of speakers. We initially published a paper that showed our experience with the first 43,230 platelet units that had been screened prior to issue. We found 14 confirmed and 21 non-confirmed positives on the initial test, for an initial positive rate of 0.8.

At that time, we were mostly using apheresis platelets, because they are cheaper and they are just as good. They are just as good and they are cheaper. However, we were moving to apheresis platelets because of the VCJD risk, and there is no doubt that if you are a patient recipient, your risk of getting an unexcluded infection from a donor depends in a linear fashion, as a multiple of the number of donors you see. We had moved to apheresis platelets, or we are trying to move to apheresis platelets.

Our rate on apheresis platelets was .03 percent and the pooled was the same and the total was the same. Now, we did find early on that our rate in apheresis platelets was the same as our rate in pooled platelets. We made platelets in a different way, and perhaps the overnight hold and the leuko-depletion made a difference. That is no longer the case.

I think it is no longer the case because we have introduced additive solution for pooled platelets and not for apheresis platelets. Although the data are not overwhelming, it seems to be that the introduction of additive solution for pooled patients had resulted in delayed bacterial growth. We are missing more on day in pooled platelets than we were before, or maybe they are not clearing as much.

We have seen some of this data before. It is more interesting to update them than show these. Our total positive rate was 0.08 percent. At day one screening, it was a little bit higher than that at day four. When we retested it outdate, it was higher still. That was somewhat disappointing.

The bacteria themselves, just for the record, because we use an anaerobic bottle, because our second bottle is an anaerobic bottle is a better way of putting it, we find a lot of P acnes. We also find CNS and those were the others in the initial screen.

I just want to draw your attention to bacillus. Even if you introduce pathogen reduction technologies, you will still have a problem with bacillus, or we will still have a problem with bacillus. They account for about 1 in 10 of most series, either at discovery or in transfusion reactions. Even if we move to pathogen reduction, we are going to have to address that issue. It may well be that there are techniques when you actually pathogen reduce that might address it, but it is still going to be there.

I also want to mention the proteus. The proteus was in a triple apheresis donation. This is important. We test every component of a triple or a double. If we collected double, we split them and then we test them. That is two 15 ml bottles for each component of a double or

for each component of a triple. That is what we do, because we are testing the product and not the donation. That is just a philosophical thing.

This proteus came from a triple. The first unit tested negative. Well, they were all tested at the same time. One of three tested positive. There were three two-bottle tests. One of three tested positive. We interdicted obviously the other two components. One had already been transfused and was fine. The recipient didn't turn a hair. There were probably no bacteria in that component. The secondly obviously tested positive. When we went back in, it was really quite strongly positive. The third had tested negative. When we went back in, it was quite strongly positive.

There is no doubt that we would have caused serious harm to one, or at least two, of the recipients of that unit, had we not had bacterial testing. Had we not tested all three, we might well have missed it. That is the money unit. For all of this, this is probably the one or two lives that we have saved.

We calculated that the false negative rate, based on the observed total positives in day one, plus the false negative rate, of which that we took as the testing on day seven, you could include the testing on day four. We thought they were probably testing the same thing or a

similar thing for a false negative rate, but not as good. We excluded the day four positive test for this, but it came out at 29 percent with a composite(?) of about 20 percent to 40 percent. That is the sensitivity of our screening results was in our hands at that time.

What is worse? The Dutch have reported something similar, as well. Twelve of those 35 contaminated units were not interdicted, and in fact, have gone into patients. Our overall screening effectiveness was only two-thirds, but no reactions were reported from those. I will go onto the reactions in a minute.

We had done probably as we had set out to do. We ended up having done a limiting dilution test that gave us some sort of notion of how many bacteria were in the initial contaminant of the platelet unit. Of the 24 two-bottle positives, remember we started off with one bottle only, and then we moved to two, during the 24 two-bottle positive era, there were 13 units that should have grown in both bottles. They were able to grow in both bottles, and none of them did. These are excluding the anaerobes, the propion.

None of them did, eight of them grew in the aerobic and five grew in the anaerobic because aerobes will grow in the anaerobic, as well. I should have acknowledged this earlier, but all of the math done at the beginning of

this were done by Larry Dumont. He gets all of the blame and we get all the credit. I just wanted to acknowledge that.

We were able to calculate that there were less than 60 cfu per platelet unit at the beginning of the contamination, in most instances. We have got a 300 ml bag with only 60 colony forming units, or growable colony forming units, in the platelet units. We are up against a real problem, but I guess we knew that.

Our conclusion at that time was this was never going to work. It was good, it was better than nothing, we thought, but we were never going to get there. We were always going to find bacteria in the bag, I don't doubt. Sampling would never reach an acceptable level of detection.

Our view, and it probably still is our view, is that if you are making a large volume of intravenous medication that is going to go predominantly into immuno-compromised people, and you can get rid of the bacteria in it, you should do that. End of story, and you should take a hit on that. You should take the loss of potency and perhaps increase the dose size. That was our view. You are making a medication, you are giving it to sick people, you know there are bacteria in it. If there is a way of sterilizing it, do it. If you lose 20 percent potency, so

what, increase the dose. It is what we did with factor eight before, a long time ago.

No matter how large the sample, unless you test the whole thing, or how sensitive the test, we had a test that could detect one bacterium in the sample, we were never going to get there. We decided, and we still do this, don't get me wrong, that we should move to something else. Apart from the morbidity, and there is obviously, that is what we are here about today, but there is loss of products and there is also the problem of recalls.

If you get a test positive, and particularly if you are making pools, you have got to recall all of the red cells. In multiple apheresis units, you have got to go and look at the recipient of the other of the sister unit, have them tested, they have to stay in hospital until the bacterial cultures are back, et cetera. There are other issues around it, but mostly it is about morbidity. That is where we were.

Now, we did actually make a strategic decision to move to pathogen reduction technology a couple of years ago. We went and tendered for it, and it was too expensive. The Germans wouldn't pay for it, so we are still doing this. But we would, we have made the decision to move.

Now, I am going to update the data, mostly around the apheresis, as to where we have been since. In spite of ourselves, we are still doing this. We have now tested from apheresis 54,000 apheresis donations. We are now up to 20 positives. One of them, so 19 on day one, and one day on four, one out of 33,000 on day four have retested positive and that is a staph capitis. We have more or less given up expiry because of the money. Those two positives were from the previous study, as well. We haven't found any more since, but we have stopped really looking in the same way, unfortunately.

These are just the data, just to show you how it is going. There is the 53,000 on the day four tests are down there, 33,000 on the end. Our false positive data are there, and these are data where, in fact, the machine gave us a reading that was not there. Our non-confirmed, which always for all intents are run about twice are confirmed are also there.

The reason 2009 is in red is that that was the year we brought in the chloraprep method. We have used diversion in place, and we have always used isopropyl alcohol chlorhexidine system, but we brought in the chloraprep as described by the Canadians and the British in 2009. It is far too early to say anything yet, but it is beginning to look interesting, that in fact our underlying

rate may have come down a bit. We will probably never get statistical significance around that, but it is interesting. It may not actually be the prep itself. It may be the additional training and the retraining that has gone into it.

These data, for a slightly different time period, but these are our latest reasonable data on pools versus apheresis. You can see now that the rate in pools has gone up. It has doubled in the last three, four or five years. We retest those on day four, as well, and we get much more in pools on day four than we do in apheresis. Again, we are turning off our production, so these are data perhaps of more historical significance.

It does show that we are getting more in pools than we are on day one, which brings me back to the point, we have changed the ecology around pools in that intervening period. They now have additive solution in them, and we are getting probably delayed growth. We are beginning to see an increase in the late detection, which is not good.

Now, we have haemovigilance system, where by there's a haemovigilance officer, usually a nurse, but it can be a lab tech, in every hospital, whose entire job it is, is to follow up the recipients of blood transfusion. It is modeled on the French system, we originally did the

British, the shop system, but we now do the French system. There is somebody who gets paid every day, to go around to the hospitals and look at the recipients of blood transfusion. We tend to get very good data. We get a lot of febrile transfusion reactions and we tend to follow them all up. They all get cultures, et cetera.

In one instance, we grew a staph epi in a platelet unit. This platelet itself had gone out, so this platelet unit had been transfused by the time the staph epi grew. We went and looked at the patient. The patient had had two platelet transfusions that day. The first one, which was not the one we were interested in, had given a febrile transfusion reaction, and that had been reported through the National Haemovigilance System.

The second one, which was the one we were interested in, had not. Quite clear, that patient would have been detected, had they had a febrile transfusion reaction. I think that is probably fair to say for all of the hospitals in the country at the moment.

I think our febrile reaction data are reasonably good. There may be one or two in there we don’t think so, but I think they are reasonably good and we can stand over them. We did have one proven septic transfusion reaction in 2001, before the haemovigilance system came in and before the testing system came in. That was reported and

discovered. Since testing, we have had none, and that also applies since we brought in mandatory haemovigilance. We are now looking at close to 200,000 with no septic transfusion reactions associated with them from that.

There is an embargo on employing people in the health service in Ireland at the moment because we have got money and we don't want them anymore. We now have some 50 or nearly 70, if you take in sort of some of the big hospitals of two haemovigilance nurses, so we have 70 nurses going around the hospitals, who are only collecting blood transfusion data. The hospital managers are looking at those with very envious eyes because they are short of frontline nurses. This system may not survive.

As I said, our view was that we would, in fact, move to pathogen activation. We have not been successful in doing that, which is unfortunate, but there we are. We continue to do this. Now, remember I said at the start that we had this peculiar demographic where all of the platelets were kept in-house, so we were able to retest them. It wasn't really any great logistic cost for us to do that.

That will have to change, because it turns out now, I should have known this before, but I have only known this since I changed jobs and I now work on the hospital side rather than the blood transfusion side, there are many

units in the hospitals which have accident and emergency units and maternity units that don't store platelets. They have to wait one to two, and sometimes more than that, hours if they want a unit of platelets for somebody that has been turned into road pizza or a post-partum hemorrhage. That is clearly not acceptable.

As on from next year, we are mandating that all hospitals with accident and emergency or maternity units have platelets. It's sort of modern medicine. It is kind of nonsense that they don't. That will incur massive costs, unless we can do something about this. We won't be able to retest those platelet.

It means that about 20 or 30 hospitals will now be taking platelets that didn't take them before, and expiring almost all of them because these hospitals do not have oncology units. There are only six oncology centers in the country at the moment. There is some shared care, but that is about it. They don't have cardiac surgery, they don't do a lot of complex surgery, but they still need to use platelets. We are now going to have to look at a system of sending platelets out, bringing them back somewhere into a quarantine laboratory somewhere, retesting them and relabeling them and reissuing them. The utility of our system is going to be questionable.

There is the issue, of course, that if you are going to get rid of the bacterial problem by a retest, and I think day four or day five retest could well do that, if you are going to get rid of the bacterial problem. Well, why wouldn't you start looking at storing platelets and additive solution beyond seven days? We hold platelets at seven days. We haven't really put a lot of effort into moving them beyond seven days, mainly because of the bacterial problem. You can store platelets for what, eight, nine, ten days. There have been good data showing them, in fact, somebody stored them for up to 14 days and still showed some sort of utility at the end of that, compared to normal day five platelets.

Once you get over that, you can start thinking in different terms. If you have got a good transport and logistics system, perhaps when you bring back your platelets and retesting them and relabeling them, validating them, you get rid of the bacterial problem, why stop at seven days? We will certainly be looking at going to eight, nine, ten days, if we have to do that.

Agenda item: Questions for Speakers

DR. HOLLINGER: Thank you, Dr. Murphy. Just for the group here, we really hold our applause for the people who are speaking, so no applause.

We have got some time for some questions for the speakers before we take a break. Any questions?

DR. DEMETRIADES: There is a lot of talk and effort to make the platelets safer after day four. I want to know what is the functionality of platelets on day five, six and seven? Maybe one of the blood bank people can tell us.

DR. ROSEFF: There has been data that it is not as good. I mean, that as platelets age, their efficacy goes down. I guess it was just eluded to that it does fall, but is that again what some people is the tradeoff for the bacterial contamination. I think that is what was just said, but there is a reduction in functionality.

DR. DEMETRIADES: This is my point. As a trauma surgeon, I don't want to give my patient platelets which are suboptimal in their function, day five, six or seven. I do not see the point of trying to extend their life beyond day four.

DR. VOSTAL: Could I also make a comment on that? There are storage systems, bags, that have been able to store platelets up to day seven. They all meet a certain criteria that we have to qualify those platelets.

DR. KEY: My question has to do with case definition. I think it was alluded to. I just want to make sure that there is uniformity of case definition here,

in terms of a death that is related to contaminated platelet transfusion. We are talking about, and the most obvious, patient gets a transfusion within minutes or hours, has a major septic shock reaction.

This issue of whether it maybe under appreciating the role of slightly contaminated platelets, let's say as a contributing cause to death, that may not be so obvious clinically, in a immuno-suppressed patient who develops a positive blood culture 48 hours after a transfusion of a smaller inoculum. Is that an issue? Is there homogeneity in terms of the case definitions, and is there a potential that this is being underestimated?

DR. JACOBS: To answer that question, there are two issues here. One is deaths are often under-reported as recognition for several reasons, including that patients who go into septic shock can be in organ failure, can be kept alive for several weeks to several months before they eventually succumb. We had one case where we only reported the death late because the patient only died five weeks after the transfusion.

Conversely, the reverse also occurs. In the 65 patients we have monitored, however, we found no evidence that low level of contamination causes problems. For example, we do see CoAg negative staphylococci causing bacteremia frequently in oncology patients. Their

susceptibility profile is totally different. They are very highly resistant organisms, compared to the CoAg negative staphylococci that come from contaminated platelets, which are typically very antibiotic susceptible, coming from the skin of health donors.

DR. KEY: The other part of the question was whether there is uniformity or consensus on a case definition, through AABB or whoever. Is this being defined in terms of what constitutes relatedness?

DR. JACOBS: I would say, and there are people with more expertise than me in this, that there is no consensus on this.

DR. HOLLINGER: Anyone want to talk from the AABB in regard to standards?

DR. KUEHNERT: There are definitions in the National Health Care Safety Network Haemovigilance Module for transfusion reactions, including bacterial infections. There certainly can be room for improvement with it. We are also talking globally with ISPT, to make sure that the definition is standard globally.

It is a difficult issue for situations like staph epi, a very common organism, requiring something like molecular fingerprinting for a definite imputability might be too much to ask. What we tend to do, or what we are planning to do, an analysis of these data, and later on in

the session, I can talk about the data that we have that we are just compiling now, is combining categories between definite and probable imputablity, basically as one unit. You certainly can stratify between definite and possible, and still get useful information by combining those two categories.

I think there are a lot of situations where you just don't know, because so many patients are on antibiotics. The patient may not grow it out, they may have a septic reaction, but not grow it out of their blood culture. It is not going to be a definite reaction, but you are fairly certain that it was due to the transfusion. I think there are certainly papers that have been published with definitions, but we do have a standard national definition that we use.

DR. HOLLINGER: I was just going to ask Dr. Murphy maybe, you said you had a haemovigilance program. Could you comment about what your definitions are then?

DR. MURPHY: Yes. Our definition of a reaction attributable to a septic blood unit, as there is bacterium in the bottle, in the sample to start with. You then recover the same bacterium from a patient who has had a febrile transfusion reaction, but that is it. The entry is that the patient has had a reaction, that that patient just had a blood culture and that that blood culture gives you

the same bacterium. We don't go on to strain definition or to antibiotic sensitivity, for example, or DNA analysis. We just take it that if we have grown the same organism, then that is it.

We may or may not find enough in the bag that the patient received to grow it out again. We don't put that in as a criteria, and you don't have to recover it from the residue of the transfusion as long as it was there in the initial culture, and it is there in the patient.

Now, you may well be stuck, and more often than not, you get clinical examples where the patient has had a febrile reaction around the time of the transfusion. There are bacteria growing in his or her blood, and you have nothing left to sample. Sometimes you have a residual left that has been sort of lying on the side on the bench for a while. Those are more difficult. We don't take those as definite cases. In fact, we would normally take those as non-attributable.

DR. HOLLINGER: Dr. Key, do you want to follow up on it?

DR. KEY: I was wondering, you had been culturing, and then you dropped doing the culture at the termination of the units. I just wondered if there were any studies that have looked at those positive cultures, and then looked at the outcomes of the patients, the

recipients, to see whether a positive culture in a day seven actually is associated with poorer outcomes. You quote two cases that were positive, I think, and no consequences to the patient. I am wondering about large scale studies, whether in fact that is an independent in a multi-varied analysis, whether that is associated with poorer outcome.

DR. MURPHY: I am not aware of any systemic studies.

DR. PIPE: Maybe along the same lines, I think we are also concerned about when central venous lines are part of the equation in patients, because if I understand the way the data has been presenting, there is probably a threshold for a febrile transfusion reaction as far as the amount of the inoculum. You could be below that and there won't be an acute febrile transfusion, but that could be plenty of inoculum to seed a central venous line, in which case the actual sepsis event may be days or sometime later. Those patients, I don't think, are being captured as transfusion related infections, because there is no timeline associated with that.

It seems to me that you would have to have some sort of, again, part of longitudinal haemovigilance, if you knew you were infusing low level inoculums that were below a threshold, you would also have to track outcomes in

patients way beyond the actual transfusion day, like you said. I think for central venous lines, it could be a significant amount of time after the timing of the infusion.

The classic example in our clinic is the patient comes in, and at the point of access of their port or their line, they crash in the clinic just with the initial flush because they have overgrown inside the port from could be many days previous when it was last accessed. There is obviously other ways that you can contaminate a port, but blood, I think, is still an ongoing issue, as a major source potentially.

DR. MAGUIRE: Just to take that a little bit further, I was impressed with a number of isolates of Proprionibacterium acnes. One, I had a question, I think, for Dr. Jacobs who mentioned that there were some septic reactions in Europe.

Then, secondly, the virulence of this organism is largely foreign body infection. Intravenous catheters, but also heart valves, prosthetic joints and whatnot. I think that would be something to think about, in terms of long-term effects, as well.

DR. JACOBS: Again, to answer that question, we have been culturing every platelet going into patients for over 20 years. I direct the microbiology lab. I see every

single positive blood culture, I see every single positive infected line. I see every positive infected joint.

There are none that we can trace back to Proprionibacterium acnes over 20 years' experience. I realize that this is .5 percent of the U.S. platelet supply for patients, but I think this is pretty representative population. Similarly, with CoAg negative staphs, I can tell you where the CoAg negative staph is coming from a contaminated line, because they are all resistant to every antibody, except vanc, whereas the ones going into platelets are all fully susceptible to antibiotics. I think you can make that distinction very easily.

Also, to address some of the issues Dr. Kuehnert mentioned, many of the definitions that are used are guaranteed cases. You got bacterimia, but in our experience again you've got 65 patients who we know received contaminated transfusions. Very few of them were bacterimic for a variety of reasons.

One other extremely important point in this whole issue is reporting is a big issue. Having definitions doesn't mean people are going to follow them. The biggest failure we found in our institution, as you saw from passive surveillance is, physician recognizes this is a transfusion reaction, treats the patient appropriately,

does not report this to the blood banks. That is not recognized and reported as active detection.

DR. HOLLINGER: You had mentioned something about the PGD test, about false positives. I never really heard, or maybe I missed it, about how you reduce the false positive. Where are they coming from, what is the reason for them?

DR. JACOBS: That is an extremely important point, and there are going to be at least two presentations addressing this later on today. Most of the false positives are from rheumatoid factor. The company is working very hard to come up with methods for reducing false positives in general.

Also, just to emphasize one point about the rapid test, that the study I showed and Dr. Haddad mentioned this, was done on the day of transfusion and that the results are available before the unit is used. There is a 24-hour window currently that the platelet is valid for, once you have done the testing.

False positives are a big issue, because the false positive rate is far higher, and many steps are in place to reduce the false positive rate. I hope the next generation test and material is also being presented at the AABB meeting next month, to show steps that are being taken to reduce the false positive rates.

DR. DI MICHELE: To that point, I was just going to ask Dr. Murphy how he handles unconfirmed positives when there is still a bag or still the potential of those platelets getting transfused, especially given that based on what I thought I heard, you actually do that testing on units that are rare and need to be used, like CMV negative units. Therefore, by implication, they are going into immuno-compromised hosts maybe.

DR. MURPHY: We treat unconfirmed as true positives. We think that they probably are.

MR. DUBIN: I would like to take it back to a larger issue. As we see more and more, especially the older guys, with ports, with comorbidities that lead to the need for platelets and other things, and nobody looks at us. We are just kind of out here. We are outside of the HTC system, many of us. Yet, I think we represent a good pool of information about this, as we age and have situations that call for platelets or red cells. I think we have largely been ignored

We discussed this at the A Plus call the other day. I just wanted to get back to that larger perspective, because I think it goes back to reporting. Those of you that know me know we have been saying this for a lot of years. We spend all this money getting systems to talk to each other, and the docs still don't really understand what

the reporting structures are. We haven't given them the guidance.

During the '94 outbreak with Hep C and immunoglobulins, I walked into a pretty predominant doctor's office I know, he used to be with NIH. He hadn't received any notification. I pulled out my list and there was stuff in his fridge that needed to be recalled. He asked me why there was no communication. I said, for us, this is a reporting issue and a turf issue, and we need to get above it. It has been our opinion for years, and we feel frustrated by it regularly.

DR. HOLLINGER: Thanks, Corey.

DR. RHEE: I have three questions, if I could just get some clarifications on this. It seems like it is a very low number overall. People who get platelets are not healthy, they are sick. The first thing is, I see a decrease in time, as far as the fatalities go. I know there was an issue with seven day platelets in the past, but if you look at the last several years, there seems to be a decrease in trend, not an increase in trend. Is it just a study that has made us aware of this contamination? From a clinical standpoint, it doesn't seem like there is a spike upward or change in the wrong direction, so that is the first question, because I am just trying to get an oversight as to the importance of this.

The second thing is the confirmed death from platelets, are they truly confirmed deaths or is it an association? I know for me, when I am in a trauma situation, when I am giving platelets, there are 10 things going on and there is never a way for me to identify which of what I was doing ultimately hurt the person. On the medical side, or if somebody with liver failure that needed platelet infusion, there are many, many things going on. Sometimes they die and they had a platelet transfused, which was contaminated, but is it confirmed that that was the true cause, not just a smoking gun.

The third question was, if we are going to try to make a decision about this testing, how much do these rapid tests cost?

DR. HOLLINGER: Does somebody want to comment?

DR. HADDAD: I cannot comment on the third question regarding the cost. Regarding the first question about the prevalence of this problem, you might not see it at individual hospitals like we see and hear reports that certain hospitals, they don’t see any septic reactions, like in years maybe.

When we need to look at the country as a whole, and certainly this remains a public health issue, and we feel there are measures that can be taken to reduce the incidence of septic transfusion reactions and associated

fatalities. There are some technologies that can address it, maybe modification of other technology. Since this is a public health issue, and we feel that there is something that can be done about it, that is why we are taking it on.

Regarding question number two, and this is the association, whether there is a causality, when we, at least at FDA, get reports, every fatality, as you know, should be reported to FDA within seven days. We have a team of medical officers, so whenever we get a report, we determine whether the fatality is, in fact, associated with the blood transfusion product. Then, we classify the fatality based on whether it is contamination of the blood product, whether it is TRALI, whether it is volume overload. We do establish causality, and only once we have established that causality, these reports are published.

DR. SANDERS: On the third question, the average price of the test in the U.S. averages about $25.00. In other words, it is about comparable to the cost of what the culture cost was, when it was added to the cost of apheresis.

DR. HOLLINGER: Just to add to that, Peter, that doesn’t take into account personnel and other costs that go along with that, too.

DR. RHEE: When we do the test, if we are going to do it on the fourth day, I assume it is going to be

about approximately 15 to 25 percent of all platelets that are transfused, right? I mean, we are not going to test every one. There are going to be millions that are transfused, but we are only going to do it on a small portion that still hasn't been used. It's like the old milk in the fridge. You are going to test it to make sure, and smell it before you drink it.

DR. HOLLINGER: Isn't it true that a couple of tables showed that there was, what, about 20 percent of samples were still left at five days, if I'm not mistaken.

DR. BIANCO: About 50 percent at day four.

DR. HOLLINGER: Fifty percent at day four, that's right. Was it 50 percent at day four? I thought it was only about 20, 25 percent across the board.

DR. KLEINMAN: I don't remember who showed it, but I think Salim did, but I think it was about 25 percent at day five. I think if you also include day four, you are going to get another 15 to 20 percent, if you look at the ABC slide. I think if we are talking about testing on day four, it is probably close to half the product that we collect. It is probably about a million apheresis platelets a year, because we collect about two million.

DR. HOLLINGER: I was just looking at the ones I wrote down here, it is 24 percent in one study on day four.

At day five, it is 31 percent and 22 percent, which is what you just mentioned, Steve, thank you.

MS. MASSARI: I wanted to make a comment to one of the questions that was just posed. My name is Maureen Massari. My six-year old daughter died three years ago from bacterially-contaminated platelets. I have been an advocate for change ever since.

The question that was posed had something to do with association. I can tell you, I have done a lot of research on this, the platelets that my daughter received were so highly contaminated with bacteria that, if they had a black light in that room, it probably would have been glowing. She received them on day five. From what I understand, I hope I use the word right, it had something to do with the donor had given a lot of platelets and it was like a double apheresis or something.

There was another child that was battling cancer who got the platelets from the same donor on day four. He had also gone into sepsis and ended up in the hospital that night. He survived because he was almost three times her age, twice her size. My daughter wasn’t so lucky.

I attribute this also to pretty poor communication between labs that my daughter ended up with platelets that I think could have, and should have, been pulled off the shelf. As far as being sick, she was almost

cancer-free. She had been battling for two years. She went skipping off to the clinic that morning before school for a routine CBC. Her blood values were good, except that her platelets were a little low, and she never came home that day.

I have been asking the same question for three years, what is changing? I think that this is great that we have got this meeting today. Thank you for this conference. At the end of today, I hope that something is really going to change, and that we have a decision at the end of today. I look forward to that. Thank you.

DR. HOLLINGER: Matt?

DR. KEUHNERT: I want to say that I think we have come a long way in the 15 years since I have been involved with this issue. I don't think we are doing enough. I appreciate those comments and that tragic story.

My question was going to be about active surveillance. I have heard that term used a couple of times already, and coming from CDC, I don't know what it means, because it means a lot of different things to different people. I am just wondering if Dr. Murphy and Dr. Jacobs could enlighten us on what they mean by active surveillance because there is epidemiologic active surveillance and there is microbiologic active surveillance.

Even within epi surveillance, it can mean different things in terms of what is actively being pursued. I think that is important, just in terms of apples and oranges, or whether we are dealing with the same definitions.

DR. JACOBS: For the purposes of bacterial contamination of platelets, we culture every platelet when it is issued. That is our active surveillance. For our passive surveillance, it is what is reported to us as patients being recognized as having transfusion reactions when we do have a contaminated platelet. Very simple.

DR. KUEHNERT: You don't go to the bedside after every transfusion and look at signs, symptoms, vital signs, all of that?

DR. JACOBS: Only if the culture is positive.

DR. KUEHNERT: Only if the culture is positive.

DR. JACOBS: That is a limitation. We don't know what the specificity is, we don't know what the sensitivity is.

DR. KUEHNERT: You don't have a transfusion safety officer in your hospital?

DR. JACOBS: Sure, we do. All transfusion reactions are worked up, and we know which ones are bacterial-associated because we have cultured everything.

DR. MURPHY: Our haemovigilance system is in fact a passive system. You have to report into it. Yes, there is somebody in your hospital who carries a bleep and they are whom you call. If we send out a unit that subsequently grows something, then we do follow that up. We get cultures, et cetera, on that patient, so there is an active follow-up, but that is not active surveillance. There is a passive surveillance. An active surveillance presumably would be culturing every recipient of a platelet transfusion, which perhaps we should do.

DR. KUEHNERT: Just the follow-up on that, so you rely on clinicians to recognize a reaction. Your transfusion safety officers, which is great that you have them, by the way, we don't have the luxury of those in the U.S., don't go to each patient actively, is that right?

DR. JACOBS: In the bigger hospitals, they do not, where most of the platelets are used.

DR. HOLLINGER: I think I am going to have everyone take a break here. We will come back at 10:45. Thank you all.

(Brief recess)

DR. HOLLINGER: Let's start the next session. We have two speakers in this section. The first, Larry Dumont from Dartmouth Hitchcock Medical Center. Both speakers will talk on the transfusion service perspectives. Larry?

LCDR EMERY: In the meantime, I was just going to announce that there will be an open public hearing later this afternoon. So if there is anyone here that wants to speak at the open public hearing it will be later this afternoon.

Agenda Item: Transfusion Service Perspectives

DR. DUMONT: Thank you very much, Mr. Chairman, ladies and gentlemen. I want to thank the FDA for inviting me down to share our experience. There are some disclosures you have heard about. I have got some relationships with some commercial forums, both present and past. Dr. Szczepiorkowski also is on the scientific board for FENWAL, who has a relationship to this topic. And the first study I will show you, Verax actually provided the test kits for that at no cost.

So who is Dartmouth? Well, we are an academic tertiary care medical center. We have got 353 beds, level one trauma, neonatal intensive care, hematopoietic stem cell transplant program. We do not do liver transplants. This shows the number of discharges for 2010.

A transfusion medicine service -- we issue approximately 8,500 red blood cells for transfusion, apheresis platelets we use exclusively, about 2,500 of those were issued per year. And the footnote there says

that includes some day 6 and some day 7 platelets. I will talk about that in a bit.

So where does that put us in the whole scheme of things? Well this shows the results from the 2009 survey of platelet transfusions in the US. And you can see that we are that tiny, little green wedge there compared to everybody else, 2,500 per year, but it is interesting to note that the hospital services, the median transfusions reported were 232, so we are actually on the high side of things for the whole nation.

So first of all, where do our platelets come from? We have primarily three sources. About 40 to 50 percent of them are collected actually in house, and what we do with those is 32 to 48 hours post collection, or if we have to dispense them before that time because of clinical need, we take a sample 8 to 10 milliliters and that is placed in an aerobic bottle. For those aficionados of BacT/ALERT, it is the fan bottle. It is actually not the bottle that is approved for this particular application. And then the product is dispensed on demand. So we take the sample, start to culture, and we don’t wait for culture results necessarily.

We also obtain platelets from a different supplier, and that supplier at 24 to 32 hours post-collection, they place 8 milliliters in a BacT/ALERT BPA

bottle. That's the one that is approved. And they release after a minimum of 12 hours negative on test. The other supplier takes a sample at 24 hours plus collection. They put four milliliters in the eBDS system, and they release 20 to 30 hours following that if it is negative on test. So that is where the platelets start from.

The objectives of our studies was, number one, to determine the preferred testing strategy for rapid bacterial tests. And we used the PGD. It was the only one available, so we used that. That is the whole presentation today. And then number two is to describe the results of the secondary screening with the PGD test.

So in part one, and this was reported in ABB in 2008, we looked at three different options. One was to test every platelet on the shelf every day. So after lunch, everything that was on the shelf got pulled off, samples taken, and a PGD test done. So the same platelet could be tested actually several times if it hung around for a few days.

The second option was to test only platelets that were Day 4 platelets, and for us that represents about half of the platelets. As we just heard we are kind of in the middle of the road on that. About half of our platelets were transfused on Day 4 or 5. And the third option was to test to order, basically, 30 minutes prior to issue. And

we had two units that were pre-tested within the previous 12 hours for emergent cases.

So what we did is, we ran each of those protocols two months straight, so that took us six months to get that done. It shows there how many tests we did. And at the end of that, we took the decision to pick Protocol B, where we tested platelets only on day four, once per day. And we made that decision because that was the easiest to integrate in our system and we felt the only option that was actually sustainable.

We did the other for two months and we made a lot of unhappy people. And, in fact, we couldn't always do it, like in the middle of the night and those types of things. We just couldn't do some of those other options, so that is why we selected Protocol B.

It looked something like this. The apheresis initial culture test was done based on site collection protocol. After lunch the technologist goes in and sets up the tests and does them. And in our shop it takes a technologist anywhere from 45 minutes to two hours to do the complete processing.

It is not just doing the test, but it is going to get the platelet, bringing it in, doing a bunch of paperwork, some computer work, taking a sample, processing the test, getting it going, recording the results of the

test, doing some more paperwork, doing some labeling change and putting it back on the shelf. So it takes some time.

The scheme was, Day 4 apheresis platelets, we did a PGD test. If it was nonreactive that was released back into inventory. If there was reactives, then we repeated that three times. And if all three were non-reactive, then that was released as a false positive and it went back into inventory. If any one of those three was positive, then that actually took the platelet out of circulation. But then we cultured that product to see if it was a true positive or not. And if it was a negative culture then we call that a false positive. And of course a true positive.

So our results for 46 months, shown here, we had a total of 8,500 apheresis platelets that we issued. We tested 41 percent of those, so again, that is about our Day 4 or 5 load. And we found 25 initial reactives. On the repeat, 20 of those 25 did not repeat as reactives, so those were false positives. And then we had five that we took to culture, and none of those came up as positive on culture.

And I will say that we have continued this scheme since April. We are still doing it. We still don’t have a true positive. The other thing we do at Dartmouth, because remember we are up north and we are in the woods, it is a long ways to everything, so we have needs for platelets.

Of these products that went on and weren't transfused by Day 5, 364 of them were transfused on Day 6 or 7 because of medical need. And the remainder of those that weren't transfused, we held onto until Day 8 when we retested them with a PGD.

So there is the summary and a table. I will note that based on Dr. Jacobs' paper we would have expected 18 false positives in our scheme, and we actually had 25. So we are in the same ballpark.

So rapid test of apheresis platelets on Day 4, we observed no true positive bacterial contaminations. On Day 4 rapid test, 59 percent of our apheresis did not have a secondary screening test with a rapid test prior to release. And we had no septic transfusion reactions identified over that period, including the six and seven day old platelets.

We do not have active surveillance, but we are a teaching institution and we have a very active transfusion medicine department. And we have residents and fellows, and we have a transfusion safety officer, and there is a lot of teaching to the clinical staff. And every report of fevers and those types of things, of course, all emphasize reported, but they generally are. Those are always followed up by a transfusion medicine physician and they are worked up for computability.

So the expected results from a PGD on Day 1 culture screened apheresis platelets, based on Dr. Jacobs' data, we would expect true positives at 326 per million. And at Dartmouth, with our testing scheme, we would expect that would take us three years to get a true positive. And we have been doing it over four years. We still only have one.

For the US hospital that is the median of the number of platelets issued in a year, we would expect it to take them 13 years. So that is part of the difficulty of making decisions at the individual hospital level. False positives are shown there about 70 days and 10 months. To get a false negative, we would expect five years at Dartmouth and 22 years at the median US hospital.

So another consideration -- because we are trying to figure out how to maximize value to our whole health care delivery system at Dartmouth. So one of the things that we are concerned about is, we are throwing away platelets after five days. And this shows the summary from the 2009 National Blood Survey. And that shows on the right, apheresis platelets that during 2008, 270,000 were outdated, of just over 2 million that were collected. So that is a 12.7 percent outdate rate.

And at the price of $539 a pop, that is over $145 million that went in the rat trap. So there is some

economic gain here if we can reduce that number. I will tell you, with a passport study when we went from five days to seven days, we anticipated, and our enrollment anticipation was based on taking a number approximately 12.7 percent, taking it down to about five percent. Well actually, it drove it way down.

In fact, some centers, it went nearly to zero, and so that actually really hampered the study because we couldn't recover those eight day old platelets to re-culture them. So making that change from five days to seven days is huge on that number.

Our conclusion is that the routine use of a rapid test at the time of apheresis release would improve the test rate. So if we tested every single one of our platelets at release. But that would also increase the number of false positive in our hands. We were concerned about that.

What we are going to propose -- of course, we will see what happens today -- but we have considered this as a transfusion medicine service and we are going to propose to our institutional transfusion committee that we would maintain our current practice of testing every platelet that gets to Day 4, and that we would request a variance from FDA to extend the shelf life to seven days

for platelets that were tested one time, on day four or day five or day six or day seven.

And since I have your attention, I get to comment on some of the question issues. The first proposal that comes up as far as moving back platelets from five days to four days, in our setting that is really untenable. We will see huge increases in outdates. And I think practically speaking what will happen is that you will just have the medical directors signing off more releases, so that we can serve the patients.

From the standpoint of doing a rapid test within four hours of transfusion, we have already done that. We have done that experiment. And we don't think that it is sustainable. The other thing to consider is, for the vast majority of bacteria -- in fact, maybe Dr. Murphy's one very slow-grower -- by Day 4 most bacteria aren't in a lot of growth any more, in these platelets. They are way up there. They are saturated. So this business of four hours, I don't quite follow that.

And then from the standpoint of doing a culture test on Day 4, that is a good thing because the sensitivity is obviously better with that. To require two bottles and another 20 mils, 10 percent of your volume, I am not sure that we need that because we would have a very sensitive test already. And we already have overgrowth if we have a

contaminated unit. So I think there would need to be some discussion around that point.

The way I think about all the numbers -- we saw a lot of numbers this morning, one out of 5,000 and 3,000 and gosh, how do you keep all those straight. In my mind I tend to remember that an apheresis platelet is about one in 1,000 chance of having a viable bacteria in it. If you apply the culture test at 24 hours, that is a test sensitivity of around 25 percent, so you are going to reduce that quite a bit. And of course you get the really bad ones. I am pretty sure that happens.

And then if you apply in this case the PGD, if we take Dr. Jacobs' numbers, we will increase the total test sensitivity, if we do both of those tests, we will increase that from 25 percent from about 70 to 75 percent with that test. Now if we did the culture test, it probably drives it even higher. But then we also have the issue of we have to wait for a time, and the difficulty on that side of it.

So there are my opinions along with the data. Thank you very much.

DR. HOLLINGER: Thank you, Larry. The second speaker then is Mark Yazer. Dr. Yazer is from the Institute for Transfusion Medicine in Pittsburgh.

DR. YAZER: I would also like to thank the FDA for inviting me to speak here today. It is a great honor

to be on this side of the rope. You might not be able to clap, but maybe you can laugh. On behalf of my colleagues at the Puget Sound Blood Center, it is nice to be here to show you this data that we generated, and it is great to see that people read the online early section of transfusion. It has only been out for a few weeks.

But we want to show you how we implemented this rapid detection at the time of issue in our centers. I also want to say a few words about how a centralized transfusion service works, to give you a sense of the volumes and how it is that we can generate large numbers in a short period of time.

The Pittsburgh model, and to a lesser extent the Puget Sound model, involves having stand-alone blood banks in each hospital with our techs and our products and our SOPs. And they do the rapid things in the hospital -- ABO typing, pooling of platelets and cryo. But they are supported by a large, off-site laboratory that does most of the routine things -- the typing screens, all the reference lab work.

You can see from this schematic here that we get our blood from a central blood bank. It all ends up in this centralized facility which is in downtown Pittsburgh. And from there we can send blood to any of our 16 or 17 hospital customers. We keep track of where the units are,

and we can move them around as the needs be. So essentially what we have are four full-time physicians looking after 16 or 17 hospitals on a full-time basis.

These are the numbers, the volume of the transfusions that we issued last year. We conceived about 115,000 red cells. And we don't do universal leuko reduction. We use it on a more selective, evidence-based approach, which frees up some money for us to do other things. You can see we did about 120,000 whole blood platelet, or platelet equivalents, of which only 14 percent were apheresis. And these would be for mainly the HLA platelets that we used for our cancer patients. And 64,000 plasma units. We also used up to five day old plasma.

These are the numbers from Puget Sound -- 74,000 red cells, about the same number of platelets, and a little less plasma. I am jealous of that plasma utilization. So in terms of the Verax PGD test. In our hands we have lab aides doing it. These are people who maybe they have a high school diploma, they are not lab techs, and so we have trained them to be able to do this test. It is a better use of the tech time to have lab aides doing this sort of thing.

For us, it takes 35 to 40 minutes. And we have worked with the company to help get that down even lower. In our situation we pooled the platelets first. The

platelets are of course leukocyte replete at this moment. We pool them, we do the test, and if the test is negative then we do other manipulations according to what the patient's special needs are. It is important to keep that in mind.

This is our study design here. You can see that between the Puget Sound and Seattle we did this study. Both of us used mainly whole blood platelets, which are non leuko reduced at the time the test is done. And again, the reason we do this is so that we don't end up wasting a filter or radiation time on a pool of platelets that is never going to make it out the door. So we do the test first, get a negative result, and then do whatever else we need to do, based on the patient's special needs.

This is where it gets a little bit interesting. Initially, when the PGD test came out, we were not allowed to repeat an initial positive result. So this is the way we tested platelets for the first 18 months or so of its use.

Obviously, if the test comes out and it is negative then the platelet is suitable for issue. It goes out the door. If the initial test was positive, again, we were not allowed to repeat it so we would send the platelet for culture, we would quarantine the co-components and culture them as well. And if it was negative then we would

send the red cells out, or the plasma back out if it was within time.

Clearly, if the initial test was positive and we grew something out of the platelet or out of the co-component, then this was a true positive and we did all the usual notifications. So this was the way things worked for the first 18 months or so. And then more recently, the package insert of the PGD test was upgraded to allow us to do repeating of initial positives. And so you can see, this is what we defined as a platelet that was suitable for issue. Either the first test was negative or the next two tests were negative. If that is a negative platelet, it goes out the door. We didn't culture everything like Dr. Jacobs did.

Of course, if the first test was positive or the first and third tests were positive, then we had to quarantine the co-components, send it for culture. If nothing grew then this was considered a false positive. And, as you can imagine, if the two PGD tests were positive and something grew in the platelet or the co-component, that is a true positive.

So this is truly a pain. However, it is important to remember that in terms of reducing false positives, having this ability to repeat the test two times is a good way to reduce the false positives. In Seattle

they did it a little bit differently. They didn't repeat the testing, even now, even though it is FDA approved. They didn't repeat it.

What they would do was, if they had an initial positive they would go back and they would prepare segment from each of the individual platelet units. And they would test, they would do the PGD test on the individual platelet units to see if they were positive or not. So the methods of culling a true and a false positive are a little bit different between our two centers, but they are quite similar.

So here is the meat. Over 36 months we tested over 70,000 whole blood platelet pools. So these are platelet pools we are talking about. It reflects about 350,000 individual whole blood platelet units. We had 249 positive PGD tests over this period of time. And you can see that they are scattered nicely throughout the different epochs over which we studied them. We had a little peak at our center about a year into the testing, which we attributed to contaminated reagents. Once we worked with a company to deal with that, you can see that our numbers have come back to their average.

The arrows indicate where our true positives occurred. So the first and second PGD test results were positive. The culture grew something in the platelet or

the red cell. And you can see that they are nicely spaced throughout time. They didn't all occur in one period. There were two towards the end of the study. So in terms of the false positives, 242 of those 249 positives were false positive, and that turns into a rate of one in 292, as we heard earlier.

This led to a monthly discard of seven whole blood platelet pools, or about 30 individual whole blood platelet units. Which we think in our center is acceptable. And don't forget, this is coming on the heels of us abandoning the PH test, which led to us discarding about 80 sterile individual platelet units per month. So we were very pleased to be able to cut that wastage down with this test.

You can see, compared to the results that Dr. Jacobs had, we had lower false positive rate. But that is probably due to the fact that we were more used to doing the test. We had been doing it for a longer period, and we had had a lot of experience at the time we did this study.

The true positives, we had seven of them. Seven of the 249 tests were actually true positives, for a rate of about one in 10,000. This is the platelet pools we are talking about, not the individual units. And this leads to about a three percent positive predictive value. We had earlier published our results. Our initial six months of

using the Verax tests, where we had a PGD of about 14 percent. But this demonstrates some of the folly of publishing results so quickly, because you can see when we tested 10 times more the PGD shook out to about three percent.

Interestingly, our rate of true positive platelet pools was significantly lower than the rate of culture negative apheresis pools at the time that they were issued. And I expect the daggers to be drawn on this at any moment.

This is some more useful information. These are the seven true positives that we had between Pittsburgh and Seattle. The first one is really interesting, because it grew not only in the platelet but it also grew from one of the red cells from the co-components that we isolated. The other seven positives that grew out of the platelet did not grow in the co-component.

However, because we did find this one, we interdicted the transfusion of one contaminated red cell unit, we think then that any test that we apply at the time of issue to the platelet is a surrogate screen for the rest of the inventory as well. So we think we get a bit of a bonus in screening platelets at the time of issue.

And you can see that our platelets were generally a little bit older, days four or days five. And these were the bacteria that we saw on the right-hand column there.

So just to comment a little bit on the lower rate, why are we seeing the lower rates of bacterial contamination in whole blood platelet pools versus apheresis platelets -- don't forget that apheresis platelets are stored in a leuko reduced state. They are not filter leuko reduced. They are leuko reduced on the machine when it comes off, so there are not a lot of leukocytes in there.

So the ability for that unit to auto-sterilize is greatly reduced. Compared to a unit of whole blood platelets that sits around for three, four, five days, the white cells that are still in there can go to town on any bacteria that happen to be there. and in fact, when we make the platelet pool there is often between a 10 to 15 minute lag between the time we make the platelet pool, and when we do the Verax test on it.

So now we are introducing a variety of different donors, white cells and other anti-bacterial elements that has some time, albeit limited to effect further sterilization before we actually do the test. And I think this auto sterilization thing is important, and I think it also explains why you simply can't take the rate of contaminated individual whole blood platelet units, and multiply it by four or five to get a contaminated pool rate, because I think doing that would disregard this biological reason why the rate is actually lower.

And interestingly, there is some data that suggests that when you filter platelets using the filters, they also remove bacteria. So it is possible that the platelets we are issuing are even more devoid of bacteria than what we detected with our PGD screen.

So in conclusion, we are two of the largest transfusion centers in North America, and we are able to implement this test with relative ease at the time of issue. So it can certainly be done. You can see our true rate of positives, one in 10,000. The false positive rate is still high, one in every 300. And that creates an administrative burden on us to culture stuff and to pull in these units that we actually need for transfusion.

But as we have heard over and over again, hopefully in the second version of the test that will be dealt with.

Interestingly, we only had 10 situations where the PGD test was positive but the platelet had already been issued because of the great clinical need for that unit. One of those units actually turned out to be truly contaminated, but it only happened 10 times out of 70,000. So we think that is -- we don’t think that is a reason not to do the test. And we are very pleased with this surrogate screen of the rest of the co-components by doing the tests of the bacteria at the time of issue.

So it is only fair to close with a slide of Seattle. Again, thank you very much for having invited me.

Agenda Item: Questions for Speakers

DR. HOLLINGER: Thank you. We have some time for questions of the speakers. It could be any of the speakers this morning. Comments?

DR. PIPE: Just out of interest, is this particular PGD test the best we have? It seems we have only been presented data from one example thus far. Are there any others that are in evaluation, or that other groups have looked at to evaluate?

DR. HOLLINGER: There is the BacTx test which someone will talk about in the open public hearing. It was just approved, I believe, in June of this year. And it is only for whole blood platelets right now. That will be discussed at the time.

DR. HADDAD: If I can answer that question regarding any other tests currently on the market, in my presentation I presented that there is the BacTx from Immunetics. It was cleared for poor platelets for quality control. We haven’t seen any clinical data yet on its use on clinical products.

DR. YAZER: And that is it. That is the reason that we are seeing this, is because it is the only test that we have that is FDA approved for use. We can’t use

the PH test any more. It doesn't come close to the sensitivity of this PGD assay.

DR. PINKOWITZ: Richard Pinkowitz from Immunetics. And yes, we just recently had the FDA clearance on our first claim. We are entering in other clinical trials for apheresis platelets and others. We are a little behind the competitor in the development but are pursuing further claims and clinical interest in marketing trials.

MR. DUBIN: I just wanted to raise it. It is more a question, we wonder if, and we see it cranking up, but for a long time it seemed like the will to clean up components was not the level of effort that went into cleaning the derivatives. Granted, we were in a different crisis, in a different time. And yet we have had the luxury generally of being in a recombinant situation, except for certain specificities.

And we look at sickle cell and others, thalassemia, and say these people are still in the water, and it has been a long time they have been in the water. We have been out of the water since really just after the IOM report, and that is over a decade ago. It seems like with our technology and our smarts, are we lacking will?

I think that is the question that came up, that I was asked on the A-PLUS call. Is there a lack of will? My

answer was, I don't think so now but there may have been. But I don't really know the answer and I would love to hear from people. We would like to hear.

DR. ROSEFF: Where is the test being done, the PGD test? Is it being done -- you are a centralized transfusion service.

(Comment off mic)

MR. DUBIN: Maybe after he is done we could get an answer on that. I just don't want to run by it. I didn't ask it for the sake of asking it.

DR. YAZER: So the question is where do we physically do the test? Generally we do it in the hospital right at the time the order is received. We make the pool and then we prepare a segment and then start doing the test. But of course, we try not to issue it until the test is ready and it is negative and all the other manipulations are done. But from time to time there is a great clinical need.

And if we don't have an apheresis that has been cultured that we can send out right away, we will send this thing out with a note that the ordering physician has to sign, indicating that it hasn't undergone the usual test, but they needed it anyway. So we do it in the hospital, and we do it at our centralized facility for routine platelet orders that aren't required stat.

Like I said, we have been able to incorporate this into our workflow. We train the techs. It is not that hard to do. And I understand version two is going to be even easier to use. So it is something that we have added with minimal pushback into the workflow of issuing platelets.

Can I speak to this question? I am not sure I really understood.

MR. DUBIN: May I clarify it? I am being asked by the A-PLUS constituent groups to answer a question.

DR. HOLLINGER: Which is what?

MR. DUBIN: Which is, has there been a lack of will to get the rest of us --

DR. HOLLINGER: A-PLUS? What is that?

DR. DUBIN: A-PLUS is American Plasma Users Coalition. It used to be the Plasma Users Coalition. And to get in line with Euro Plus and C Plus for Canada we moved it to A-PLUS. And I am being asked a question that I don’t have the tools to answer. And so I don’t want to just be subjective with you. And Celso said maybe you could give us an opportunity and not make us feel guilty. And I want you all to know that is not their goal. They are asking for answers. And I have committed to try and bring answers back.

DR. YAZER: I can tell you that the Air Force through DARPA just invested a lot of money and a lot of time on a project to try and turn cord blood stem cells into mature red cells. We are working on some fundamentals now that we didn't think were going to be an issue. So it is not over, but we didn't achieve the milestones in the timeline that they had set out but it is still being funded. So it is not like we are not trying.

MR. DUBIN: I would say we were pleased to hear of DARPA's involvement and we were briefed a couple of days ago by the staff at the advisory committee. But this question still came up. I will give them the DARPA answer because I think that is one piece of it, and it is a good one, no question. But the question will come up again, guaranteed.

DR. ROSEFF: I just want to ask a question. Maybe it is more of a question to think about. I have spoken to our clinical microbiologists, our epidemiologists in the hospital. And with all of the technology going toward amplification and PCR and increasing sensitivity, increasing automation of molecular based testing, and the costs coming down dramatically as years go on, I do want to bring that up, if we really are worried about this.

I think that the false positive rate shouldn't be minimized. It really is an issue, even in a big, academic

medical center where we still have days when we are biting our nails with seven doses of platelets in the trauma hospital for the region because of a confluence of the worst case scenarios of use, the testing center has a problem with their tests and they can't release that day, and it is a week where we have had a slightly lower number of platelets that were collected.

So I think that is an issue. And I think that if we are really being serious -- and I don't want to say that good is the enemy of perfect or perfect is the enemy of good, but still we have technology. It sometimes concerns me that through all these years we have not found different platforms that keep getting brought to the table for us to look at, that can't really optimize what we can do for the best safety of the patients.

DR. JACOBS: Excellent question. I have asked myself that question many times. And if you look at the literature, there are dozens of methods that have been described to detect bacteria and platelets. At the upcoming AABB meeting there is a group in Wisconsin that has been using PCR to test their platelet inventory since 2004.

There are dozens of methods out there but I do want to make this point, that only two have been commercialized and received FDA approval so far in the US.

There are a couple in Europe as well. So the question is not technology. It is money to develop these, is the issue.

DR. HOLLINGER: And I guess cost to utilize, as well.

MR. DUBIN: But for us, cost is will in some way, and they go together.

DR. DEMETRIADES: One of the speakers suggested extending the shelf life to seven days. Now from the sterility point of view this might be feasible, but in reality seven days old platelets are ancient. They have lost most of their function. I think you would be doing a disservice to the critically ill patient. It is the same story with the red cells. We can transfuse red cells, three, four weeks. But in critically ill patients, if you transfuse red cells older than two weeks it is a disservice. We increase significantly organ dysfunction, et cetera. So I would caution you about this.

DR. HOLLINGER: Can someone answer -- because Demetrius has brought this up, and specifically again about the function of platelets at six, seven days and so on, compared to platelets at an earlier time period. I know we have talked about it, but please try to answer his question.

DR. JACOBS: When we approve storage systems for platelets we have certain criteria. And whether that storage system is for five days or seven days, those platelets that are stored out to those time points still have to meet the criteria. And their criteria include in vitro testing, to make sure that the pH stays up at about 6.4. The activation level of the platelets, and we also request in vivo radial labeling studies that monitor the recovery and circulation of platelets after transfusion.

So seven day platelets did meet those criteria when they restored out to seven days in specific bags.

DR. BUSH: I just want to add to that, there is a recent paper -- Dell Truesly(?) is lead author, published in Blood. It was an analysis of the PLATO platelet dosing study, a large NHLBI funded study, that looked at any influence of age of platelets as well as ADO type, et cetera, on the careful measurements not only of clinical efficacy but of actual platelet efficacy in terms of bleeding time. And there was no effect of the age of the platelets up to day five on clinical efficacy.

DR. HOLLINGER: But the question, I think, that he asked was about Day 7. Do you have an answer to that?

DR. WAGNER: I just wanted to mention that I think there is a tendency to think that the molecular methods are the most sophisticated and therefore the most

sensitive. And in this case, it is not necessarily the case. One of the problems with platelets, as we have heard this morning, is sampling error. And unless you are going to extract 8 mls or 15 mls of material from platelets and put it in a small enough volume to do NAT testing, it is unlikely that you are going to have a sensitivity that is the same.

DR. DUMONT: I just want to address the seven-day question, because I was involved in a lot of those tests that Yazer spoke of. And certainly as platelets age, you can do something to measure how they are a little more activated, or their response is a little reduced. And some systems, that is quite significant.

But for the systems that are approved right now in healthy volunteer studies they did very well. We have done CCIs in patients. Mike mentioned the PLATO study. I don't think there is any argument that as platelets get older, something changes. But certainly out to day seven for platelets stored in plasma right now, we have a lot of evidence to support that they function well. And certainly at Dartmouth, in our hands clinically, they function well.

DR. BUSH: On the molecular testing, the German Red Cross, Michael Schmidt's group, they do have a Paul Ehrlich Institute approved PCR testing strategy, and they have done a lot of work to get rid of the problems inherent

in contamination of reagents with bacterial sequences, et cetera.

But because of these issues of sampling, they are actually required to recast at four days. So that the same problem comes up, whether you use molecular tests that bacteria can grow in, and in order to detect them, you need to retest again in order to maintain safety.

DR. HOLLINGER: To come back to Dr. Demetriades again, did you get your --

DR. DEMETRIADES: No, there is good evidence and we discuss it in trauma all the time. Old red cells, old platelets should not be given to the critically ill patient because they are associated with a higher incidence of organ dysfunction. It is not a controversial issue, at least in the trauma literature.

DR. HOLLINGER: Do you have a response to this? Or something different?

DR. BIANCO: I will try. Actually there are lots of studies, particularly on rat cells, and the NHLBI is funding several very important clinical trials in this area. The evidence comes from observational studies. Very little comes out of clinical trials, blinded clinical trials. And in terms of platelets, there are many less studies but there are a few studies done by Dr. Sherrill

Slichter in Puget Sound in Seattle that shows clearly that the platelets have good characteristics up to 14 days.

And there are other studies. We are going to hear some showing that even not entire, not live platelets but lyophilized platelets have haemostatic function. What you want is haemostatic function and bleeding function. And those are the characteristics that are still there.

For the red cell, yes, there are many papers and a lot of questions about the quality of cells after 14 days or older red cells. But it is not exactly like stale bread. They still work partially, at least. But I am aware of all the concerns. I am aware of the concerns that came initially from the military in their experience in Iraq and in Afghanistan. This is under serious investigation.

DR. RHEE: In the trauma literature we are discussing the age of blood products all the time. And there is no good clinical evidence because it hasn’t been done yet, where we are just now recognizing these problems. So if you take liquid plasma, for example, that has never been thawed, in five days the platelet count is reduced by 50 percent. The microparticles are increased. The thrombosomes and the lyophilized, thrombosomes and the platelets are being heavily investigated now to see if

there is a way we can extend these shelf lives, because it is an issue.

And I know that we currently set a bar and then we can reach that bar with five days, and sometimes even up to seven days. And I don't mind the old blood products as long as they give them to someone else as patients and not mine. But if it comes to mine, I prefer the fresh stuff all the time.

But if you go to the blood bank, if they gave you fresh stuff, the old stuff goes away. It is just like in the grocery store. If you want the fresh milk you have always got to reach in the back because they always put the old, expiring stuff up front because you obviously won't buy it. So what we are talking about is quality and quantity. We are here talking about something that happens where we have 30 events a year, 30 to 50 events. I know they are under-reported. So let's magnify it and say 300 events a year with bacteremia.

We have 1,000 lightning strikes a year. Lighting strikes are pretty rare. So we have got to put all that into perspective. If we really want to take a good product and make it better, I am all for that, if we could do it effectively. But when we also do that and extend the days out, we also have to know that the functionality of these platelets are not yet fully understood.

Right now our bar is okay, and we have been able to reach that bar, but I think the science in the future decades will show you that we have to find better ways of doing things. And what we have been doing with the old stuff is not necessarily that good.

DR. BIANCO: You made some very good comments and very important. But I think what we are missing here is a little bit of a picture of what happens to a platelet, and how long it takes to get where it goes in terms of timing. The platelets from apheresis are collected at some site in a blood center different from a hospital that will collect them, but in a blood center.

They will reach a central facility for manufacturing that will prepare the unit, will test the unit, and it will be ready probably 24 hours later. At that point, the platelet has sat for a sufficient time to do the first culture. And that culture is done, and centers will wait between 12 and 24 hours for these, to call it negative at this point and release the platelet to a hospital. The platelet is transported to the hospital, rarely a platelet will be transfused before Day 3. And so, everything happens between Day 3 and Day 5.

In some systems, for hospitals, for instance, a little bit farther away, that will not have a small trauma of volume in all that, blood centers will send them the

fresher platelet that they may have. It may sit there for one, two days, and then in the last few hours, the last day, they will bring that platelet to a larger hospital with a big trauma center so that the platelet unit is not wasted.

It is a very difficult logistic system, and even when the attempts to extend the life to seven days, it addresses the availability issue, and so that the platelets are there for the patients that need them. We have Saturdays, we have Sundays. So platelets on Monday and Tuesday, particularly Tuesdays, are a very difficult product to have. I ask people at the hospitals to maybe confirm that. So changes in the dating of the products, platelets, very short life, are not easy to manage.

And the testing -- that is the other point I wanted to make -- that is, the Puget Sound and Pittsburgh are among the largest centralized transfusion services in the country. But in the rest of the country, or most of the rest of the country, there are a few. There is a good one in Tampa, for instance, and all that.

But most blood centers and hospitals, they will ship all the products that they have to the hospital. So they are in the shelf of the hospital. So the testing by the PGD is something that will have to happen at the

hospital at day four. It is not effectively done by the blood center.

And actually, I will ask later in the afternoon when we discuss, there is really the FDA is trying to ask the blood centers to deal with the issue of doing rapid test before four hours, or before the platelet is released for transfusion. But how can we deal with it when actually the FDA doesn't have immediate control over the hospital. They have control over the product and what we do in our blood centers. So I think that is another interesting question that we will have to deal with.

DR. MURPHY: I think the red cell age issue is going to run and run. I am sure it will be back before this committee many times. But I am unaware of any data that even would force you to take a precautionary position in relation to older platelets. The data that are there -- and they are good -- suggest that seven day platelets are haemostatically effective.

In a trauma patient, as we heard earlier, there are so many things going on that you cannot possibly distinguish between whether a five or a seven day platelet is better or worse than a three day platelet. You can make inferences, but the data that are there -- and there are good data in bleeding haemostatic patients with no

platelets -- that indicate that seven day platelets are good, are as good as two or three day platelets.

That is it. You can't discount those. I admit, in a trauma patient you want to take a precautionary position. You have to practice parsimonious medicine. There have to be platelets for everybody. We can't buy these things. We have to convince our donors that we are making good use of their gifts. And that is the reality. I'm sorry.

If the data were such that we had to take a precautionary position, believe me we would be taking that position. But they are not.

DR. STRONCEK: A little bit different question. One of the questions that we will address later on is, is it just simply cutting the shelf life to four days rather than five? And people have done mathematical modeling. If you change the outdating of red cells, what would that do to outdating and supply? Is anybody -- there is nobody here that is going to present later on about what that would do to platelets?

What would it do to the outdating? It is not completely obvious from the tables you show here what the outdating would be. And then the other problem is that the supply of the platelets then is only available for really

day two, three and four. So would that have an impact on the blood collection centers and increase the cost?

And then the third question I have is a little bit different. It has to do with if we do the rapid testing, yes, big blood centers have shown they can handle it pretty easily. Medium-sized academic centers will handle it. But what happens to the place that transfuses one platelet a week? Will they be able to do that? Will that have any impact?

DR. KATZ: Louis Katz, America's Blood Centers. I just changed jobs. We have actually just approached a couple of the manufacturers. The briefing documents from the FDA came out rather late, and we hadn't anticipated quite the emphasis on four-day platelets that we saw. So we are going to try and engage in that modeling very quickly to figure out the impact of a four-day platelet on what is happening.

I can tell you, however, that in my stinking little blood center out in the middle of nowhere, formerly my blood center, we drive three million miles a year, rotating stock to drive our outdate rates to below five percent. And a four-day platelet is going to change our entire model. And we know it is going to drive it up above 10 percent, but we don't know if it is going to drive it to 20 percent or what.

We have a very good sense that about 40 percent of our platelets are transfused on day five, and you saw just a tiny amount of that data on that one slide that Salim showed.

DR. YAZER: In aggregate we are huge. But some of our centers are really very small and don't transfuse very many platelets. Clearly it is more than one a week. But the maintenance of the proficiency that we found, even with the tests that tend to stay at the smaller volume hospitals is quite high, when we test them to see how well they are performing.

It is an easy thing to do. The test is easy, it doesn't take very long, it is not a complicated thing with a bunch of different re-agents. And so I think that would be the standard for any other test to come along to be developed, would be, to be as easy as the one that we have now. So in our experience we found even our smaller centers, having the tests maintain their proficiency is straightforward.

The other thing you could do, of course, you could have if necessary apheresis platelets that have been cultured on the chance that you can't get that, hold that platelet out fast enough. But in a small center like that, you would probably still want to have something at the time of issue.

DR. PIPE: I just wondered whether there is any metric that has ever been tracked or is known within some of the blood banking systems on deaths attributable to lack of access to platelets. Is that something that is monitored within hospitals? Within blood banking centers? Is there a way to track whether, even with the current dating, it looks like it was about eight percent wastage even with the day five. So are there any known numbers in the background of death that can be attributed to lack of access to blood components?

DR. BIANCO: We find a way. It is a very difficult number to comment on, and I am not aware of deaths because of lack of blood components. We find a way to get them. And if I don't have it I will call Dr. Gilcher and he will find a way to, even if it is to find a private pilot from these services to fly that unit to where it needs.

There is a lot of exchange among blood centers. There is a lot of movement of blood components around the country. And we have been able to deal with shortages very easily. And actually, we are in a very comfortable position these days. We have plenty of blood and blood products.

MR. DUBIN: It begs the question a little, and I want to say this. I came on this committee the first time

in 1996 when we had this discussion. And there is concern, and I am always told it is about the dollar number. I would remind people what the fractionators and the derivative folks did to get us out of the water, and how quick it was done. And of course, they saw greater profits and they were driven.

But it was done very quick, and I don't know how to answer component people when they come back at me on a call and say 16 years later, where is the quickness, where is the will? We are still in the water. And I like what I hear today. It is important. And I honor that you guys and Ron fly stuff. It is not about shortages. It is about other communities looking at us and saying, you guys got out of the water, why are we still in it?

I would challenge everybody to at least consider that thinking as part of their look at it.

DR. HOLLINGER: We are coming down to time when we are going to have to go to lunch. Larry and Jay, pertinent, straightforward responses.

DR. DUMONT: Just quickly, I don't know of anybody at Dartmouth that has died because they didn't get platelets. Nobody has exsanguinated. However, I will tell you that since the PLATO study has come out, and we run into platelet shortages all the time and if we don't have them in our blood bank from us, it takes three hours to get

it. And so we are dividing a lot of products. We are taking a regular dose and we are cutting it in half, just to be able to supply the needs. So we are in a continual supply challenge.

DR. EPSTEIN: I just wanted to clarify the legal situation of regulatory oversight of the transfusion service. I think what Dr. Bianco was alluding to is that if a transfusion service doesn't collect blood and doesn't further manufacture beyond separation of plasma and compatibility testing, then the inspections are by deemed organizations under CMS.

However, the transfusion service is fully regulated. They must comply with FDA requirements. So I think the regulatory question is whether we would regard the additional testing -- for example, using rapid tests or an additional culture -- as further manufacturing that would trigger the licensure requirement. But if not, it would be the same system where they must comply, but where the inspectional oversight is through CMS.

DR. HOLLINGER: So it is 11:45. We are going to take a break until 12:45. We will all be back here and start the afternoon session with the open public hearing at that point. Thank you.

(Recess for lunch)

A F T E R N O O N S E S S I O N

Agenda Item: Open Public Hearing

DR. HOLLINGER: We are going to go into the open public hearing. We have several people who are speaking. I will try to give their names ahead of time.

(Administrative remarks)

For the open public hearing, both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with your sponsor, its product and if known its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the

beginning of your statement, it will not preclude you from speaking.

(Housekeeping remarks)

I am going to read a couple of names so you will know who is coming in order. Allene Carr-Greer will begin first, and then Dr. Benjamin, Dr. Tomasulo, Dr. Fitzpatrick, Dr. Yomtovian, Dr. Metzel, Dr. Levin, Maurine Massari, Dr. Berg, Dr. Lousararian, and Melanie Osby and Michael Allen. We will go in that order and it is all going to take place over there. So Allene Carr-Greer for the AABB, please.

MS. CARR-GREER: Good afternoon. I am Allene Carr-Greer. I am an employee of AABB. I don’t have an association with any vendors. AABB thanks you for the opportunity to speak today. We also wish to thank the Food and Drug Administration for addressing the issue of bacterial contamination of platelet components in a public venue.

AABB has addressed this issue on several fronts during the past decade, and we appreciate the opportunity to provide a record for this meeting of the actions AABB has required member facilities to take to limit and detect bacterial contamination in platelet components, and of education provided to the membership, to support

implementation of the various requirements and recommendations.

AABB strategies have been developed using expertise of members of the association and they are listed in the statement. The method for AABB policy and requirements to be communicated to accredited members is through publication of association bulletins and development of standards.

The current requirements of an accredited AABB member applicable to today's discussions are published in the Standards for Blood Banks and Transfusion Services, the 28th edition, and are printed. I am not going to read them in their entirety. These standards were also applicable in the former edition, which was the 27th.

So we do have under the caption of Sterility, that aseptic methods shall be employed to minimize the risk of microbial contamination of blood and blood components. And this addresses equipment and solutions and single use equipment shall be used whenever possible. 5.1.5.1 is frequently mentioned, and this is that blood banks and transfusion services shall have methods to limit and to detect or inactivate, for those XUS members, to inactivate bacteria in all platelet components.

5.1.5.1.1, which has advanced beyond being an interim standard to a standard -- detection methods shall

either be approved by the FDA or be validated to provide sensitivity equivalent to FDA approved methods. 5.1.5.2 goes on to say that when true culture positive results are obtained then that something must be done with these results. They must go back to donors and/or be reported to physicians.

Under 5.6, with blood collection, blood has to be collected into sterile, closed systems. 5.6.2 was an important step a number of years ago, and it actually I think is our only standard where we say shall not, that something shall not happen. Green soap shall not be used, and that is in preparation of arms for venopuncture.

5.6.2.1 was that diversion pouches were introduced into draw lines, or the end let line. Diversion pouches will be used for collection of platelets, including whole blood from which platelets are made.

So AABB early strategy focused on moving the membership away from the use of green soap to prepare venopuncture sites and toward the use of pouches that divert the first milliliters of blood withdrawn from the donor potentially containing a contaminated skin plug into tubes used for testing, rather than flowing into the collection bag.

The standard 5.1.5.1 was published in 2003, and was effective in 2004, and practically the result of

implementing this standard was detection of bacterial contamination in apheresis platelets by culture based methods. Eventually this included pre-storage pulled whole blood derived platelets as well. Remaining whole blood derived platelets were evaluated using a variety of methods. This included the use of pH and glucose readings, as well as observation of swirling. These were the conditions in the middle 2000s.

Association Bulletin issued in 2003, this was called further guidance on methods to detect bacterial contamination of platelet components, was a comprehensive document that provided the membership with background information on the risk to recipients' safety posed by bacterial contamination of platelets, and the underpinnings of the approaches that had been considered to limit and detect contamination.

It provided practical guidance on the implementation of some of the techniques and provided sample plans and algorithms. In 2004 there was another guidance -- Actions Following an Initial Positive Test for Possible Bacterial Contamination of a Platelet Unit. And this Association Bulletin is still in effect for members who need that assistance.

In 2009 this was the bulletin that introduced -- 5.1.5.1 was introduced in 2009. It reviewed what was then

the current status of technology available to meet the intent of 5.1.5.1, provided an update on new technologies in development that would offer an alternate method for meeting the standard. It also informed members that once studies demonstrated the efficacy of an alternate method in detecting bacteria in whole blood derived platelets, AABB would likely adopt a more prescriptive interim standard.

Then there was the interim standard 5.1.5.1.1, and that was announced in May of 2010 and became effective in January of 2011. This standard was subsequently published in the 27th edition of our standards. Then we followed that in August of 2010 with suggested options to help our transfusion service members comply with the 5.1.5.1.1.

The point of that was to move the transfusion services away from use of surrogate testing, the pH and glucose, to culture-based or rapid immunoassay point of issue bacterial screening. Another option they could choose was use of approaches or methods that, while it was not FDA cleared, they were validated to be of equivalent clinical sensitivity to an approved or cleared assay.

Because AABB recognizes the remaining residual risk of bacterial contamination in apheresis platelets, the association welcomes guidance from FDA on ways to reduce

this risk. Multiple approaches, in addition to those proposed by FDA today, require careful consideration.

Any further actions, however, must be validated as to their efficacy and impact on patients who depend on platelets for treatment. No changes should be advocated in the absence of a careful evaluation of the impact on platelet availability.

DR. HOLLINGER: Thank you, Allene. Next speaker, Dr. Benjamin from the American Red Cross.

DR. BENJAMIN: Thank you. I am Dr. Richard Benjamin, Chief Medical Officer for the American Red Cross. It is an honor to address the committee. The American Red Cross distributes over 850,000 apheresis platelets per year. That is more than 40 percent of the national use of apheresis platelets. I want to point out that I am on various scientific advisory boards, but today I am speaking for the Red Cross. I am not speaking for any other companies listed.

I want to elaborate on some of the data that Dr. Haddid spoke about earlier from the American Red Cross. Over a five-year period from January 2007 to the end of December of last year, we tested over 2.2 million apheresis collections using the BacT/ALERT culture system. That is anaerobic bottle only, 8 mls sample taken between 24 and 36 hours after collection.

We distributed over 4 million platelets after splitting. Through our passive haemovigilance system, we have had 38 reports of probable or definite sepsis, including four fatalities. The rates listed here for sepsis and fatality are our current quoted rates, one in 107,000 for sepsis, and one in 1 million for fatality.

Please note this are underestimates. These are passive haemovigilance for distributed platelets. So it doesn't take into account the wastage that occurs. And also, we use a definition of sepsis which excludes any minor reactions or patients that are exposed to bacteria and do not react. So this is a lowball estimate.

The bacteria involved are mostly staph coag negatives. And we have had one fatality from those, so watch out for them. But we also have staph aureus, a major pathogen, some streps. Three gram negatives, the klebsiella, enterobacter and acinetobacter. Don't forget the gram negatives are coming through. In fact, we had two septic reactions last month to a split product of apheresis products. So they are still a problem.

We have had one clostridium. This is in fact the only report that I know of, of an apheresis platelet associated with clostridium perfringens. The other two reports in the literature were not apheresis platelets. So this is the first report of those. So it is a risk.

The major point is that most of the reactions occur on Day 4 and Day 5. Fatalities, two on Day 4 and two on Day 5. If we restrict platelets to four days, we will only solve half the problem of bacterial sepsis. Indeed, if you want to retest with BacT/ALERT systems, you really need to do it on the evening of Day 3.

The other observation from these data is that the Day 1 BacT/ALERT culture really only gives you two days of safety. So if you do it evening of Day 3 re-culture, I don't think there is any data to say you can get to seven days. I am confident you can get to five, but I am not confident we can get to seven.

Note also that if we look at when the Red Cross distributes platelets to its hospitals, if you think about it, we take our sample for BacT/ALERT on the afternoon, on the evening of Day 1. We wait 12 hours to release them the morning of Day 2. They go out of our door lunchtime Day 2, half of them in fact, almost half of them go out on Day 2 afternoon and Day 3.

So if we limit platelets, or if we retest in the evening of Day 3, they are already in the hospital. We do not recycle platelets back to the blood center or between our hospitals as other blood centers do. We have no control of those products, and in fact it will be very difficult for us to get those platelets back for re-

culture. So we do not think that is a viable system at all.

In fact, if faced with four-day platelets, we may be pressurized by our hospitals to release platelets earlier so they have more time for use. So that our current 12 hour hold after the inoculation may in fact have to go away. We may have to start distributing them straight after the inoculation. And some blood centers do that. So please think very carefully before moving to a four-day platelet.

Just comments for the record. If we are going to do re-testing with BacT/ALERT, it should be on the evening of Day 3. We really only have a two-day window of safety. These cultures would have to be performed in the hospital and not in the blood center. Make a point that there is little evidence that we need anaerobic testing. In fact, the false positive delayed positive rate with anaerobic testing is five to 10 times higher than aerobic testing, and it will put this system into the same range of false positives as we have heard about the PGD test.

A point about point of issue testing -- really we would like to see that performed on the day of transfusion, on Day 4, 5, 6 and 7, if we think that is a viable proposition. The restriction to within four hours of transfusion is impractical and not based on data. And my

conclusions are bacterial culture testing really has improved the safety of platelets tremendously. There is a residual risk. It is mostly gram positive, from false negative tests.

Limitation to four-day shelf life should not be undertaken without extensive exploration of the impact on inventory and availability. We do support the extension of shelf life to seven days contingent on day of transfusion rapid testing. And re-testing would need to be performed in the hospitals after a full impact analysis.

DR. HOLLINGER: The next speaker, Dr. Peter Tomasulo from Blood Systems Incorporated.

DR. TOMASULO: Thank you for allowing me to make some comments. I am the Chief Medical Officer of Blood Systems. And my principal goal today is to urge you to add to your consideration five-day shelf life with a larger volume of proportionate inoculation in the aerobic bottle. We have already initiated this intervention and we are working on how we can monitor it. Certainly we will follow the rate of true positivity. But getting the data on the outcomes is a little more difficult. We are going to monitor as best we can.

The basis for this recommendation I think is that I believe that blood centers in the US can do more than they are doing, and that they should. The increase in

volume can be implemented. There is some expense to it, but it can be implemented in a CGMP fashion, and it should have an impact.

In the issues paper, the statement was made that the impact is theoretical. And I think, while I agree that it isn't possible to predict that the increase in detection will be sufficient to reduce our concern about the safety of platelets to zero, I think we can predict that we will pick up more bacteria and there is no reason to conclude that we will only pick up non-pathogenic bacteria. So we should have an impact.

Blood Systems is also willing to consider later testing strategies, similar to the ones that Dr. Murphy described, or even later testing strategies that would have us testing a portion of our platelets on Day 1 and providing a two and one-half day from release period of safety. Day 2 with a two and one-half release, et cetera. These are obviously complicated and we would need good process control to do that. But we are considering how we might do that.

Just to make the point using a mathematical model of why we are enthusiastic about our proportionate model testing, at Blood Systems we issue a tiny, tiny number of platelets compared to Dr. Benjamin. We issue 150,000

platelet a year. And we test them all right now, up until August, with an 8 ml sample.

We have had an average of 10 true positives every year. And if you back calculate from the assumption that there are roughly one in 1,100 positive platelets on collection, you come up with the contamination level of five CFU per bag. Now I don't suppose that every contaminated bag has five CFU. But that is the conclusion you would make using the mathematical model.

So at five CFU per bag you are on a very steep curve for an increase in sensitivity. And we predicted that we would double our true positive rate by going to the proportionate testing and inoculating 3.8 percent with each collection procedure.

I said it was easy to do and there was some expense. When we began this evaluation to do this procedure, the initial cost estimate was that it would increase out total platelet manufacturing cost by five percent. And we decided to move ahead with that. And then as always happens, you try to figure out how to reduce that cost.

By using larger sampling devices and other maneuvers that I am not able to describe, we were able to get the cost down from that. And we implemented the testing during August last month, with no price increase.

And so we have announced the change to our hospitals without a price increase. And we are hoping to gather data that will support five-day storage of those platelets.

A point I would like to make is that while we in the US have all generally been inoculating between four and eight or 10 mls, the practice in other countries is quite different. This is the result of a very informal survey and I have probably got some of the data wrong. But in general, everybody inoculates more than we do. I don't know why we got to where we are. But it seems like this is an example of things that we could do in the US that we are not doing today.

I think that Ireland and parts of England are the only places that do what I labeled proportionate testing, even though all the centers do larger volumes than we do in the US. To further try to quantify the impact of this -- and Dr. Jacobs, I apologize for getting the number of cultures done wrong on this slide -- Dr. Jacobs explained the culturing that he did as part of his study, and Dr. Murphy just described his four-day cultures.

I looked at just the last two years of Dr. Murphy's data, which had 12,000 apheresis platelets in it. And Dr. Jacob's 10,000 apheresis platelet. You can see that the true positive rates are very, very low in both. But maybe the increased volume being cultured in Ireland

has produced a benefit in the situation for the platelets being screened later.

So in sum, it is our thought that we can make improvements in the blood centers. We are willing to test increased volumes, and we can do that and feel that we can continue to operate with good process control. We think we can also test later. We are not delusional in that we don't think this is going to solve the entire problem. But we think it is an improvement and that the FDA may want to consider making large volume inoculation the basis for all the future options that you consider.

Because it seems it can be done very well in other blood centers and we are sure we can do it in the US if they can do it in Ireland and England. Thank you.

DR. HOLLINGER: Thank you, Peter. The next speaker, Dr. Mike Fitzpatrick from Cellphire. Is he here? Okay. The next speaker, Dr. Roslyn Yomtovian, from CWRU.

DR. YOMTOVIAN: I am here from Cleveland Ohio, Case Western Reserve University and the VA Medical Center. So I will speak primarily about the clinical significance of coag negative staph. I will go through some of the slides quite quickly and I will speak a little quickly. Please refer to your handout for more information.

To put this in context, it is hard to put more than 20 years of experience as a professional dealing with

this problem, and more than 10 years as a patient. And I will talk a little about that, my experience, into five minutes. But I will do my best. The next slide are disclosures. I have no equity in any of the companies that I have consulted for. And this is available for everyone to look at.

I am going to emphasize some particular goals, and that will be the clinical significance of coagulase negative staph, which is all too often considered innocuous. But in many instances, especially in susceptible patients, it is a cause of morbidity and mortality. I will share some personal comments on platelet bacterial contamination, particularly testing, and my view of cost effectiveness based on my experience as a patient.

Now it was alluded to by Dr. Jacobs, we started on this sort of soap operate of platelet bacterial contamination in 1991 when we had a cluster of four cases. And this was ultimately reported in MMWR in 1992. Our cases occurred all in a one-month period. I do want to say these cases cluster. So one of the points that was made earlier about predicting how many cases a small hospital may have, it may be faulty if you consider that clustering does occur.

We have seen it. I know when I have looked at Hopkins data, they have seen it. And one has to keep that

in mind. If you look, you have seen this before, but this is to emphasize that it is quite variable, the number of cases per year. On average, there were four cases per year. And I will say that fever onset was delayed up to 22 hours in 10 percent of cases. I will have more to say about that in a bit.

And nearly 75 percent of cases were coagulase negative staph. The period where we stopped active surveillance, there were no cases. You have seen this before. This just once again emphasizes, we have done a pretty good job -- not perfect -- on gram negatives. But we have done a poor job with the early culture on eliminating the gram positives. So we have work to do. And I hope some of that work is done today.

We have seen this before. To emphasize, bacterial growth is highly variable, especially when there are small numbers of organisms. This was shown elegantly many years ago with data presented at a BPAC meeting by Dr. Joanne Ahio(?). And this obviously accounts for our inability to select organisms, which was mentioned in an aliquot intended for culture, and therefore detect platelet bacterial contamination early in the storage period.

Turning very briefly to clinical significance of coag negative staph -- in this one study from Florida in bone marrow transplant patients, confirmation of sepsis was

associated with gram-positive organisms in the majority of cases with one-third being coag negative staph with a mortality of about nine percent. So this is not a trivial organism.

And in a study of bacteremia due to staph in France, about one-third were due to coagulase negative staph with a predilection for patients with indwelling catheters, and/or malignant disease. And they had a mortality of 20 percent. So it is an important organism.

To just quickly go over this, there is something called phenol soluble modulins, or for short PSMs. And this is kind of believed to be the gram positive or the staph equivalent of endotoxin, that you would see in gram negative organisms. There are two cases from our collection. I am not going to read these to you, I am just going to highlight some points.

First of all, in both of these cases there was a delay in the onset of fever and symptoms. There was varying platelet storage ages. One was three days old here, one was four days old. And there was a relatively low number of organisms leading to symptoms. In one case there were only 100 organisms per ml and in the other, 10,000.

So you can see symptoms with smaller numbers of organisms. This work is early work from the predecessor of

the FDA, CRBA Institution from the Biologics Control Laboratory, then at the NIH under the US Public Health Service, which showed in a rabbit model injected with organisms which they received which had been isolated from plasma and blood products, a delayed febrile response with coagulase negative staph compared to gram positive organisms.

A word about cost of platelet bacterial testing. In the context of hematopoietic stem cell transplant. I want to emphasize that hematopoietic stem cell transplant is a very expensive procedure. And if you look at AHRQ, Agency for Healthcare Research and Quality Data, it is the procedure that has increased most rapidly in cost, from 2004 to 2007.

My own personal costs in one year were over one-quarter of a million dollars. It is a very expensive investment. So shouldn't platelet transfusion recipients be further protected from platelet bacterial contamination at a relatively small cost.

I am going to skip these. You can read them. But, I do want to end with this slide. On a personal note I wish to thank the FDA for your commitment to a safer blood supply for all US citizens, bring the occurrence of platelet bacterial contamination into the forefront by your many educational forums and discussions, including today,

your continued commitment to advocating platelet safety, so in my other role as a patient who has received platelets, at a small cost in the context of my total transplant therapy, I will have the added reassurance that the platelets I receive will be even safer.

And finally, consideration of a near issue test for platelet bacterial contamination, which provides maximum reassurance, from a patient perspective -- I am putting that hat on -- of absence of bacteria closest to transfusion. Thank you.

DR. HOLLINGER: Thank you. The next speaker, Dr. Peyton Metzel from Fenwal.

DR. METZEL: My name is Peyton Metzel. I am obviously conflicted since I work for Fenwal Incorporated, who is the sole marketing partner of Verax PGD. I have two slides, so that's the good news. And I am not going to go and read through these facts. You can see them all yourselves. These have been shown and reiterated many times over the course of this morning.

It is a little bit dangerous when I only have two slides because I have been known to leave script. Having been 30 years in the industry first starting a career as a young tot at Abbot Laboratories, up until this point in time I have been solely involved in the safety of the blood supply. For me this is a passion I have carried with me

through various companies, and finally most recently at Fenwal.

I have been lucky enough to serve on the AABB Transfusion and Transmitted Disease committee for a couple of years, and saw the struggles that all of the organizations share as they try to improve the safety of the blood supply. I find ourselves in a very unique position today actually because as we stand here today during the course of 24 hours approximately three therapeutic doses of platelets will be transfused to patients that are bacterially contaminated, that made it through the screening process. Three of them.

And for the grace of God -- and unfortunately we are going to here a very sad story in a few speakers -- not all patients survive those contaminated platelets. So for me it is a defining moment, I think, for all of us sitting in this room to take that opportunity to change the course. Like I said, I feel very passionate about this. This is an opportunity where we have a chance to improve the safety of the blood supply.

I could share a couple of instances where people known to me had relatives in the hospital that were receiving platelet transfusions after they too had gone through a serious illness, a transplant. For me to hear that, and know what the risk is, and obviously I don’t add

to their family's consternation about their loved one being in the hospital, but to know the risk and know that there is the opportunity to reduce that risk, to me it has been very frustrating.

I hope that we take the opportunity today, number one, just as FDA did with Trolley, to issue a safety notice so that physicians that are not as keen observers perhaps in every case of haemovigilance are aware of this risk and made aware of this risk so that they can be aware of it and respond to it, should it occur. And then to formally begin that guidance document, moving that forward. Thank you.

DR. HOLLINGER: Thank you, Peyton. The next speaker is Dr. Andrew Levin from Immunetics.

DR. LEVIN: Hello, my name is Andrew Levin. I am President and Scientific Director of Immunetics. We are the manufacturer of the BacTx Rapid Test which has been described a bit earlier. First, the BacTx test was cleared by the FDA in June 2012 for leukocyte reduced whole blood-derived platelet pools as a quality control test. We do have clinical trials underway now to extend the indications to cover apheresis and non-leukocyte reduced whole blood derived platelets.

To give you some information on the test and how it works, it is a single test which detects all bacteria including aerobic, anaerobic, gram positive and negative

strains. Turnaround time is less than 45 minutes from sample preparation to final result. Sample volume is half a ml, and the assay sensitivity, which I will show you in a few slides, is in the range from 10 to the third to 10 to the fourth CFU per ml. Lastly, it makes use of an electronic system to read the results and produce an interpreted final result within 30 minutes.

The methodology relies upon a new principle, which is the recognition of peptidoglycan by peptidoglycan recognition proteins which turn on an enzyme cascade resulting in a chromogenic change which is detected by the electronic reader. The procedure itself is very simple. It involves a few simple laboratory steps that can be carried out in about 15 minutes, and then the sample reading period of 30 minutes which is automated by the electronic reader.

The kit which we produce and are making available includes a set of reagents, the electronic reader and Windows software, which is operated on a dedicated laptop PC which is supplied along with the reagents and reader. The Windows software allows the user to input the tracking information on the platelet bag. It handles the reading and interpretation of the sample automatically, and it outputs a final result as pass or fail. It provides a hard copy and an uploadable digital copy.

This assay is a kinetic assay in that at higher levels of bacteria in the sample the assay responds faster. And so for highly contaminated platelet bags, with 10 to the sixth CFU per ml or more, detection would be complete in about 15 minutes rather than 30. And in terms of sensitivity, I believe Dr. Haddad presented the same information, which was part of our FDA submission.

I just want to highlight that the staphylococci, staph aureus, staph epidermidis strains are detected at higher levels of sensitivity than the average. They are detected in the 10 to the third CFU per ml range. Also, several anaerobic strains including clostridium and propionibacter are detected in the 10 to the third CFU per ml range.

Interestingly, a series of clinical isolates which came from the studies that had been reported earlier by Dr. Jacobs were tested in the BacTx test and the sensitivities for all of these strains are in the same range as the ATCC strain. So we see comparable performance with clinically derived isolates as with the ATCC strains, including coagulase negative staphylococci.

While our existing claim covers use of leukocyte reduced whole blood drive platelets, the preliminary data that we have collected on apheresis platelets indicates that the same assay sensitivity is observed for all of the

strains tested originally in the whole blood drive study, coagulase negative staphylococci, staph aureus streptococci, et cetera, all in the 10 to the third to 10 to the fourth CFU per ml range.

The specificity of the assay in the study reported to the FDA over 400 negative platelet units was 99.8 percent, which is comparable to what has been reported at least in some BacT/ALERT studies. And the time to detection in a spike study shows that at low levels of inoculant and platelet bags, the test is able to detect bacteria within a 48 hour period, in this case, in 159 out of 160 inoculations for a range of bacteria.

So lastly, BacTx provides a new solution for point of issue platelet testing for bacterial contamination. And thank you again for allowing me to present this information.

DR. HOLLINGER: Thank you. The next speaker, Maureen Massari.

MS. MASSARI: Jessica was diagnosed with cancer two weeks before her fourth birthday, in December 2006. Her first round of high dose chemo was the day after Christmas. Exactly one year after her diagnosis, she was almost cancer free. Her prognosis was looking good, and she was living a quality life. She did all the things that

little girls did. She was not only surviving, but thriving.

Throughout 2008 Jessica received regular cycles of low dose chemo to maintain her steady progress. One morning in January of 2009, she kissed me goodbye, because I had to go to the office and she needed to go for a routine CBC. So she climbed into grandpa's car and went to clinic. The platelets she received that morning were contaminated with bacteria. I never saw her awake again. She went into septic shock and by that afternoon she was on life support.

The antibiotic she was given killed the bacteria, but the damage to her body continued. Unbeknownst to me at the time, she was suffering from total organ failure. After nine days of fighting for her life, she had a massive stroke. The next day we took her off of all of life support. After she was placed in my arms, she took her last breath.

My sons believe their sister was given bad medicine. And in a way that is true. I attended the July 17th AABB sponsored conference on bacteria tested platelets and spoke about the real impact on patients who receive contaminated platelets. For starters, one would think that a compromised immune system would naturally be taken into

consideration when receiving platelets since it lessens their chances of recovering should a unit be contaminated.

Admittedly, the under-reporting of incidents tells you that the problem is more common than you know. With cancer patients the risk becomes even more substantial. One in 250 cancer patients receiving platelets receives a contaminated unit. That is unacceptable. We have all heard of effective ways to reduce this risk, but not unless action is taken.

Technology exists today to improve safety standards, but it is clear that despite awareness of the issue and potential solutions, hospitals will not act on their own. And I assure you I know this first-hand. I have been battling this on the front lines for the past three years.

The risk that is being taken is avoidable. The people here have the power to make a change and recommend immediate regulatory action to protect patients. Jessica paid the ultimate price due to inadequate testing. She didn’t get a second chance. Improving safety standards will not bring her back, but it will give others a better fighting chance, and everyone deserves the same opportunity at life. Thank you for allowing me to come here and speak on behalf of all patients who will be receiving platelets tomorrow, and in the days to come. Thank you.

DR. HOLLINGER: Thank you, Ms. Massari, we appreciate your comments very much and share with you. The next speaker, Dr. Mary Berg, University of Colorado.

DR. BERG: Hi. I am Mary Berg. I am the Medical Director for Transfusion Services at University of Colorado Hospital. And just as a point of disclosure, the expenses for my travel here today was paid for by the Verax PGD people. Okay, so I am biased, I admit it. I am here today because I care about the incidence of bacteria in platelets.

Every day I deal with platelet transfusion issues, platelet inventory issues. It seems to be a constant juggle to have enough in but not too much in, so that we don't be outdating the platelets that we are seeing every day. But I also trained at Case Western Reserve University with Drs. Yomtovian and Jacobs. And some of those cases that you saw on the slides that they showed earlier were cases that I saw during my residency and fellowship.

But also, when I went out to practice -- and I was at the University of Arizona for six years -- I had another case, a very dramatic case, of bacterial contamination. And this is the sort of story that you have probably heard before. The patient received a platelet transfusion, developed a fever, the transfusion was stopped

after she had gotten about two-thirds of the unit. The unit was sent back to the blood bank, and they paged the pathology resident on call to say do you think we should culture this unit? The patient had a febrile reaction.

And he said you know, it's just a one degree temperature rise, I don't think we need to do a culture. They paged me three hours later because the patient was coding, and they were asking for a second platelet transfusion when they had not done a post-transfusion platelet contact with the previous one.

And of course, our platelet inventory was tight. So they were like, do you think we should do this? Do they really need another platelet? So I checked it out, and it turned out that the patient was coding, they didn't know why, they thought maybe she had bled into her head, they had a huge differential diagnosis. And so I said yes, you can have the platelet. And I called the blood bank techs and I said go ahead and culture that other platelet, let's see what is going on here.

Well, at that time that type of a culture was considered a quality assurance activity. And so the gram stain wasn't done until the following morning. But as soon as the first shift came into micro I got a frantic page from a micro tech saying that it was absolutely teeming with gram negative rods. I immediately turned around and

paged the patient's doctor to say what we had found and he was absolutely floored.

He knew that you could have bacteria in platelets, but he said I thought they were all skin flora. Where did these gram negative rods come from? Well they came from the donor, but that is a long story. Bottom line was we gave this patient a huge bolus of gram negative endotoxin. She suffered multi-system organ failure and died.

So you can imagine, there was a huge response to this. I can't tell you how many hours I spent in meetings, talking to everybody and their cousin about bacterial contamination in platelets and what are we going to do about this, and all of the extended possibilities for how this could be handled. And even though we said, well you know, our blood supplier is going to be doing the gram stains and cultures on these units before they get to us, the hospital administration said that is not good enough. You need to do something in house.

Well at that time there wasn't a Verax PGD or a BacTx test available that we could do. So we started doing a pH on every platelet unit, and we did a gram stain and culture for any unit that had a pH less than 7.0. Among the meetings that I went to, to talk to people about this situation, I went to many of the nursing staff meetings up

on the BMT unit because those nurses had no idea that this sort of thing could happen.

I talked to the nurse who administered the unit on three separate occasions. She was very upset. She felt personally responsible for the patient's death. And ultimately she quit her job because she just felt like she couldn't hang another unit of platelets.

Since then I have moved on to the University of Colorado. And when I was given the opportunity to participate in the post-market surveillance test for the Verax PGD I was very happy to do that. We didn't find any true positive units. We had a few false positives. Interestingly enough, they were all traced back to the same donor.

And ever since then, I have been recommending that this Verax PGD test be put into the budget every year. And it hasn't yet been approved. In all fairness to the hospital, we have been buying new refrigerators and freezers to replace old ones, we have had to buy new serofuges. So it is not as though the hospital hasn't been putting money into the blood bank. But it just hasn't been enough that they have considered it a high enough priority to implement this type of testing.

So coming back to my bias, I am dealing with platelets every day. I am aware of the issue of bacterial

contamination. And I go up and talk to people about it whenever I can. But I really think that a place like UCH is not going to implement something like a point of issue test until either there is an incentive for them to do so, to say that there might be a benefit for them, so like extending the out date would be one reason why they might consider it.

Or, they actually see a case of their own where they have to deal with the trauma of dealing with the family and the staff and everything when you do have a fatality related to bacterial contamination.

DR. HOLLINGER: Thank you. The next speaker, Dr. Jim Lousararian from Verax.

DR. LOUSARARIAN: Good afternoon. My name is Jim Lousararian. I am President and CEO of Verax Biomedical. Since it has been mentioned several times this morning I will confirm that a second generation PGD test with improved specificity, broader reactivity and simplified processing, is in verification testing. More information about this will be at the upcoming AABB conference.

I would like to present some additional information and data in support of three points. Bacterial contamination is a public health issue. As Dr. Jacobs has presented, we have demonstrated an actual clinical use and effective solution. And, as a public health issue, policy

action is required to address the problem. So as for the first two points -- it is true that many hospitals running the PG test have not detected a positive unit.

But, as this slide shows, highly contaminated apheresis units continue to be detected and interdicted before transfusion using the test. This data was reported to us voluntarily by hospitals using the test to test apheresis platelets on the day of transfusion. Interestingly, of the five true positive units shown here, three were on day three.

As this slide shows, false positive rates, both in terms of initial reactives and repeat reactives, in both SDPs and RDPs, are substantially better in the hands of experienced users as compared to the post market study data shown in the FDA's issue summary that was covered earlier today by Dr. Haddad.

So can a day of transfusion rapid test be implemented? Will this testing impact platelet availability? As this slide shows, in a survey of 50 current users, the answers are an emphatic yes. PGD can be implemented. In fact, day of transfusion testing is currently being performed using the test in more than 100 US hospitals.

And no, there has been no effect on platelet availability in those hospitals. In general, so long as

outdate rates exceed false positive rates, which they do by a very wide margin in the US, false positives will have little or no effect on availability or supply.

In conclusion of this section, this slide shows the highly contaminated apheresis units detected using PGD both from the post market study and that we know about from the user reporting and from the prior slide. As you can see, bacterial contamination is a patient safety issue on days 3, 4 and 5, rather substantially.

Now I would like to present some data from a recently completed survey showing why policy is needed now. This was an independent telephone survey of 83 hospital transfusion services. In total, these institutions transfuse over 224,000 SDPs annually, which is more than 11 percent of the US platelet inventory. The sites in the survey purchase units from a wide range of blood center suppliers across the country.

And as you can see from this slide, there is significant confusion among hospitals regarding the labeling of current bacterial QC tests. And nearly half the sites interviewed believe that platelets distributed by their blood centers have been screened and released. So while the prior slide shows confusion as to regulatory status and possibly terminology, although screening and release are well-accepted terms in this area. This slide

is more disturbing. Over two-thirds of those respondents think that culture tested units are actually free from bacteria.

As was covered by Dr. Haddad and just a few minutes ago by Dr. Tomasulo, some blood centers are proposing implementation of enhanced culture sampling. To my knowledge this is a relatively recent suggestion yet there is already widespread awareness in the hospital community. There is also widespread awareness of the possibility of secondary testing in the hospitals.

However, look at the likely response of hospitals to the suggestion that their blood center will implement enhanced culture sampling. Nearly 70 percent then report or answer the question that they are then less likely to implement in hospital testing. So in summary, bacterial contamination is a significant risk to patient safety and has to be treated as a public health issue in order to mitigate the risk.

We have demonstrated in actual clinical use an effective and practical rapid test for use close to the time of transfusion. We urge the FDA to issue a safety notice as soon as possible and to begin the process of issuing guidance on this topic. Thank you very much for allowing me to speak today.

DR. HOLLINGER: Thank you. The next speaker who was asked to speak was Melanie Osby.

DR. OSBY: Hello, I am Melanie Osby. I am a physician at Keck School of Medicine at USC. Thank you for allowing me to speak and I apologize that I don't have a handout or a PowerPoint for you. I do need to disclose that I am supported here, my travel arrangements and my hotel costs, all of that stuff, is covered by Verax Biomedical.

I participated in the post-market surveillance study that Verax Biomedical had. And I have to say that we had some issues in trying to participate in this study. The only way that our hospital would participate is if I did all of the testing personally. So I myself took on testing about 700 of our platelet apheresis products. And I can tell you that we did find one positive, so one true positive. So we did prevent transfusion of that contaminated unit. That was pretty significant.

We had to end our study at that time because we moved to a new hospital. Basically what I need to say is that even though we know that this test is definitely necessary we are not able to implement it because our administration is just not seeing the relevance of this kind of test, especially when we are only finding maybe one positive per year, if that many.

So there is definitely a regulatory reason to implement this. I also want to say from another perspective, I am a microbiology director as well. There was some talk of possibly the micro service taking on the cultures. I work at three different facilities and we have about 20 to 30 platelets on the shelf at any one time. If we were to culture each one of those platelets -- most of our platelets are transfused at three to four days -- we would be talking about 13,440 cultures per year. Which almost equals what we actually culture for our patients.

And so we don't have enough instrumentation, first of all. We would have to actually acquire the BacT/ALERT system or the EBDS system. A lot of hospital services do not have those particular instruments that are FDA cleared for this purpose. So I just wanted to make sure that I commented on that point.

And then also for my role as a director of Hemocare Corporation, which is a blood donor center, we culture all of our platelet at 24 hours like everyone else. However, we are only using four mls of volume at this time to do our culture. So we do see a possibility of increasing the volume that we are using.

The thing that we have to think about with increasing that volume is that we would decrease the amount of platelets that are available because suddenly our double

and triple units would become single or double units, respectively. There are a lot of things, I think, to think about.

I just wanted to end with, none of these options beat having release testing. I think that testing at release is probably the only way to know whether or not we -- we might not catch them all, but we will prevent transfusion of the majority, I feel, of contaminated units. Thank you for your time.

DR. HOLLINGER: Thank you. The final person who has asked to speak is Michael Allen from Equal Voices' Committee of 10,000.

DR. ALLEN: My name is Michael Allen. I am the Executive Secretary of Equal Voices. It is a small, non-profit grassroots patient advocacy organization that works closely with the Committee of 10,000. Since 1997 my father, a member of the original DHHS Board of Blood Safety and Availability, has been a member of the Board of Directors of CTTS(?).

I have sickle cell disease, and I actually want to address participation as canaries in this coal mine. Someone brought up the issue of contaminated ports in our community. In our community we have many different vectors for infection. Many in our community are on chronic

transfusion therapies which may require various types of ports.

The issue of infection has always been an unseen and unknown variable for us, and trust has always been an issue. There are some additional symptoms with my disease that have nothing to do with infection but are more so about education and support. All we ask of this community is, as you make your recommendations you consider how much trust we have, that you do not put us or anyone else in harm's way.

We have learned in the hemophilia community to be ever vigilant and to be a willing participant in our care. The decisions and reasons behind your recommendations are never translated back to the patient. This relates to the issue of trust in our community. The people who were infected trusted the hospital and the system, that they were safe. That's all I have to say.

DR. HOLLINGER: Thank you. That ends the people who have asked to speak. Is there anybody else in the audience who would like to address the committee at this point? Not seeing any, then we are going to close the official open public hearing, and open this up for committee discussion. And the questions for the committee.

Agenda Item: Open Committee Discussion

DR. DEMETRIADES: One of the speakers suggested to extend the shelf life to seven days because of concerns about supply. Now we heard earlier that in Germany they reduce it to four days, in Japan to three days. How did these countries cope with these changes? Anybody have any information? Thank you.

DR. ROSEFF: I can't say I know a lot, but I know that when you look at international studies of blood use, the United States is one of the highest blood users, when you compare it to other countries in some of the studies. I don't know if that is because we have a different community of patients, but that seems to be a theme that sometimes gets brought up, that we are more users.

DR. DEMETRIADES: The person who made this recommendation to extend the shelf life was the Director of the American Red Cross. He might want to comment on this concern.

DR. BENJAMIN: Let me just correct one thing. My understanding is the Japanese Red Cross don't have three day platelets, they have 72 hour platelets, which means end of Day 2. So actually they start on Day Zero is their Day 1. So they are supposed to not have inventories of red cells or platelets. Everything goes from the blood center every day to the hospitals. They have a very, very

efficient system of from the blood centers to the hospitals that doesn't exist in the US.

It is a different geography. It is a way more expensive system that they have in place. So they have inventory control, they have the logistics. We do not have that. I think that is a very different system. I can't comment on the German system, although I do know that the four day restriction has created a lot of strains on their system and they are working very hard at a day of transfusion test, either PCR based or other systems they are working on. So they are also looking to extend back to four, five, and six and seven days based on testing.

DR. PIPE: I had a question specifically related to testing on the day of release and testing within four hours. If I understand testing on day of release, that would be 24 hours minus something. So I thought we heard some presentations that testing at request was just not possible. It was not doable in a typical blood banking environment.

So is there any more comment from our own membership or other blood bankers? Because I thought we saw evidence of a 40-minute turnaround for this testing. Is the within four hours of release really an impracticability?

DR. HOLLINGER: Anyone want to comment on that who is using it? It sounds like there are several that have used the product. But as you said many of them are used on a daily basis they are doing it, instead of within four hours. Can someone respond to Dr. Pipe's concern about turnaround and the ability to do this well?

DR. YAZER: Mark Yazer from Pitt. Infrequently, maybe two or three times a week at our biggest trauma center, we have to send out a unit of platelets where the Verax testing is incomplete, and the physician has to sign a release form that indicates that it was an urgent clinical situation and they accept the platelets.

The test incubates in the background and if it is negative, then that is fine. If it is positive, we try and intercept the platelet before it is transfused or at least interrupt it if it is being transfused. We saw one of our seven true positives, it actually came from one of those units that was issued on an urgent basis.

But that is the infrequent situation. That is not what happens in the vast majority of the times. Usually for the routine orders, or even for the orders that come in more quickly, we can get the whole platelet turned around in 40 minutes. And that usually doesn't create a problem, clinically. We would never deny the release of a

platelet to somebody based on the Verax test, that's for sure.

But again, it is infrequent in our situation that we have to send it out without the test being complete.

DR. BIANCO: But that is in a system where you control the inventory, you control the transfusion service. When you go to a hospital, it depends on a blood center, that is the majority of the country. You think that it is practical. I would ask Dr. Roseff or Dr. Becker to make a comment.

DR. ROSEFF: I also want to say that at the AABB workshop, the FDA workshop that we had in July, there was an interesting discussion on take downs from the same institution as Dr. Jacobs was there, and had different results from the test, a higher false positive rate than he had.

The question becomes, too, if you are able to dedicate staff to just do the testing, it is a different environment from when you have technologists in a hospital who are releasing products, irradiating, answering the phone. And speaking to other people who have used the test and have abandoned it other than Dr. Downs, they do talk about it taking longer than they have heard published, and that they have heard from all users.

So I think that there is a variability in users out there, too. I think it would be very difficult to do this on an on demand basis.

DR. JACOBS: Just to make that point -- you made several points that I was going to make -- that our institution did put this test into place in our blood bank for a year. It was done once a day. This was stretching our resources. It was very difficult to do this once a day, seven days a week. And there was no way we had the resources to do this any more frequently than once a day.

DR. DUMONT: It is a similar story at Dartmouth, although much smaller. The way staffing works, during the day you have more people from Monday to Friday. Third shift, weekends, holidays, you may have one person or two people or you may have floats covering an area, and they are covering everything. So you have got an ED case and you have got a surgical case that is going bad -- they have got to cover all of that.

So the total load, if there were infinite resources and an infinite number of people, you could do it. But in our setting the decision was, we just couldn't sustain it.

DR. SHEXNEIDER: I would be reluctant to use 40 minutes of our time or an hour of our time or maybe even a little bit more than that for either patients who need

patients urgently, someone who comes in and is suddenly found to have an intracranial hemorrhage or bleeding in the OR.

I would also be reluctant to use that for our elective outpatient transfusions in our hematology/oncology clinic. We have folks who come sometimes a long way. Those of you who are in this area know that they struggle to find parking. They get to the hem/onc clinic, they have a CBC, they need a platelet transfusion. And they frankly feel like they are waiting quite long enough to get the blood products from our blood bank. I certainly wouldn't want them to wait another hour or so, so that we could do additional testing on our platelets when I feel that we have an adequate system with our culture at this time.

DR. KUEHNERT: I have got some things on my list here. I just want to address some of the things that have been brought up by the committee so far. One of them was about risk, and if we are considering the risk appropriately. One thing that is missing in the US is a risk assessment paradigm for transfusion threats. So it is a difficult question on what is acceptable.

I would say that if this were a viral pathogen that we were talking about, and if we were talking about risk of one in 5,000, one in 10,000, there would be a panic. There is no panic here because it is bacteria. But

I would say that if someone dies from staph aureus or someone does from HIV, it is still a death. So there really should be no difference in terms of that. So I wanted to say that.

The second issue, related, that was about cost. I know this committee is not supposed to consider cost. But if you, in addition to considering the test and the resources to do the test, also consider the cost of taking care of a septic patient, the cost of a lawsuit, the cost of the media onslaught and the publicity, because I have had to deal with these investigations.

And if a medical center has not seen it, they are not considering any of that. When they have seen it, they are completely on board with screening. So that is another thing to consider. The issue here is that it doesn't happen often enough for every center to understand the issues.

Concerning the issue of active surveillance and recognition, I think that is very important. There is nothing in here as far as questions to the committee about clinical education. But I think that is a very important aspect that the committee should consider. I don't know if FDA can address it, but we certainly have seen for other pathogens a 30-fold difference between what is modeled to happen and what actually is reported to public health.

I have some data from NHSN, from the two years that we have been operating the system and have data from 2010 and 2011, and there were, out of 150,000 platelets under surveillance, five pathogens that were definite or probable reactions. They were all severe. One resulted in a death. And they were all either staph aureus or coag negative staph except for one, acinetobacter. So we are seeing a similar profile as to some of these other systems.

But the rate is a little higher. If you do the math it is certainly higher. And we think it is probably in reality about 10-fold higher if true active surveillance were done where every patient were chart reviewed for reaction after transfusion, which is how I define active surveillance.

So just quickly, my other points were that I think we need to consider some of these options here in terms of whether this is actually feasible to operationalize. But certainly additional testing needs to be done. The other aspect to it -- there are so many variables here -- is for culture, the volume of sample.

It seems to me that more volume is better. It is not only about proportion, it is just more volume. So when we have done investigations looking at this, it just seems that using either an aerobic or an anaerobic bottle, or two aerobic bottles, gives a better yield than just using a

smaller volume. And so to me it is not as much about aerobic or anaerobic. It is about volume.

So those were my main issues I wanted to get out before there were other comments. Thank you for listening.

DR. RHEE: I think if we say that they need a test, or we regulate a policy that they need a test on the third or the fourth day, it is going to be expensive, it will get passed on to the hospital and then to the consumer. And if we want a better product then I think we need to do it. I think we are not supposed to worry about the risk benefit or the cost benefit analysis. But I don't see how you can make decisions without that in mind.

So it is just like the drycleaners, that they can do your shirts in one hour, and some places it takes them three days. The same number of shirts, but they still have figured it out. And I think they eventually will figure out a system. For example, if a person comes in and you need to reverse their coagulopathy or stop their bleeding, then I think that you give them the fresh stuff.

You don't have to wait for the five day old stuff. If they have a low platelet count, and you just need to increase their numbers up, those are the ones that you could probably use the five day old, if they have been tested. So one of the issues is that when I look at the questions, I think that testing it on the third or the

fourth day, around that time period, is something that I am going to agree on because it makes sense.

But what I am concerned about is why in addition to that are the questions written in such a manner that they are adding on this seven day thing to it. Right now if it is five days and you are worried about bacterial contamination and you want to measure it on the third or fourth day because it makes the most scientific sense, then I think I would agree with that. Then that would be something that we would just go for.

But this addition of the seven day extension that came in, I think, is a problem for me.

DR. KEY: My point is a different one. I just want to get it for the record that are we satisfied that there is no significant inter-operator dependability of the test, the Verax test? I am taking it that everyone is assuming that is not a problem. Even the simplest tests sometimes are a problem. I think Dr. Roseff implied that this might be an issue. And then we heard that high school graduates can do it.

They can probably do it if they are doing it repetitively. Is there any issue about the reliability of the test? Or person to person variability in results?

DR. HOLLINGER: Wasn’t there some data presented about some tests one, the same samples done at three

different places and so on? Didn't one of the speakers present some data this morning or this afternoon about samples that were sent out and three different laboratories tested those samples? Or did I miss that somewhere? I thought somebody did that.

DR. YAZER: I don't think it was me, but there was a German study by Fulmer and colleagues where in Germany they spiked apheresis platelets and they sent them to three different German laboratories and they had a grading scale for how positive the Verax test would be, how positive, how strongly the band appeared. And it went from 0.5, which was the weakest visible, to 4 or 5, which was the strongest possible. And there was very significant variability, especially on the low end.

Some centers would give it a 0.5 plus and others would call it negative. So on the low end it was very subjective in this particular report in Vox Sanguinis from last year.

MR. DUBIN: I wanted to just build shortly on what you said, Dr. Kuehnert, because over the years we have continued to raise the risk landscape in the discussion between physician and client and the education of the physicians. It is the one recommendation I would remind people of the Institute of Medicine that collects dust on the shelf. We would urge, in the light you talked about,

Matt, that that really be looked at. Because we think we are missing something there. Thank you.

DR. ROSEFF: I think when we talk about risk, too, what concerns a lot of us in the transfusion services -- and again, this isn't just my opinion but a lot of people I have spoken to who aren't here today. And that is that we are going to trade risk, that if we do a test that uses our resources that is, again, some people say this is not an easy test to do in the middle of doing other things, that all the other safeguards that we have put in place to protect blood safety and the blood supply are going to be moved.

So our tech who gets distracted because they are doing the Verax test while they are supposed to be irradiating, may forget to irradiate, and that may not get caught. So I am concerned that we are not going to reduce all risks. We may raise some risks while we reduce others.

I think that is something that is discussed in hospitals in general when you look at safety interventions. That has been discussed in our risk management system, in our hospital, that you have to be very careful when you think that you are addressing one risk that you may have downstream effects of creating another risk that may actually be worse than the risk you are preventing.

The other thing is, someone mentioned, too, that with those who used it they didn't find that this was a problem. Well many of us were asked to participate in the studies by Verax, but we didn't think we could do it. We could not fit this entire current process. So it may be that that is a biased group of people who are saying they can do it. They were already saying they could do it when they agreed to participate in the studies.

DR. BIANCO: The other problem that I see is that we are discussing it as if we introduced this test, we were going to reach zero risk, that we would eliminate the problem of bacterial contamination. The difference between bacteria and viruses is that for the viruses, the virus is there. Either we detect it or we don't.

The bacteria in these 10 minutes or one-half hour or two hours or five hours that we are there, they keep growing, they keep dividing, and the platelets are stored under conditions that favor bacterial growth. So even with the Verax, if we look at the results, we may have a reduction. But the reduction is not that we are going to have saved lives for sure, that we have a guarantee that a patient. It is an incremental change. And so we have to take it into consideration in the whole picture.

DR. JACOBS: Again to make the point, and this was the challenge I placed when I gave my presentation --

using this test was the most successful near test(?) study ever done.

DR. SANDERS: May I offer a comment? Joe Sanders, Verax Biomedical. Just a couple of comments on workflow, in that SISIP(?) participated in a study. There were 18 hospitals that participated in the study. At the time they did that, we had very little clear understanding of the laboratory workflow and integrated the test in it. And it was left very much to the individual institutions to figure that out.

Subsequent to 5.1.5.1.1, which really compelled folks to confront the issue of whole blood risk with a more sensitive test. We had a large number of hospitals come forward to utilize the test, not because they had some predisposition or interest in a particular topic, but they were compelled to by what was going on relative to the standards.

And many of those hospitals, over almost 150 of them, many of them whole blood users, have implemented the test without any predisposition that it was easy. In fact, most thought, oh my God, we have to add another test. That is almost invariably the response of the folks in the lab. And so we have been fairly attentive in going back to those folks and understanding, now that they have had to

implement a test that they didn't have to do before, what was the impact on the lab.

And frankly what we found when we directly go back to those folks and survey them, is that they were able to implement the test without adding labor, they were able to implement the test with more help from us in terms of workflow, because what most do is, they do the practical accommodation of the reality of how they run their transfusion service.

They run a batch first thing in the morning, they issue units from that batch during the course of the day. If they need to, they may run another unit later in the day or in the afternoon, it looks like, if that is going to be a heavy day. In fact, the users who use the test out there in routine use, about 70 percent of them batch or batch and then follow with another run perhaps later in the day, or even on the night shift if they need to.

And they have been able to implement it without really any significant impact on their workflow or in terms of additional labor needed. And they have told us they actually find it is actually fairly easy to do. So I would separate a little bit some of the feedback from early on, that we went out and we were doing studies and post-market surveillance and going into sites just trying to get a study started, to the practical implementation in the real

world, when people are actually trying to integrate something in their workflow. And I think we understand a bit more about that now and can help them do so.

DR. KLEINMAN: Steve Kleinman, AABB. I just wanted not to contradict what was just said, but to give another piece of information. AABB conducted a survey of member institutions about their policies with regard to bacterial testing. And one of the questions we asked towards the end of the survey was, do you transfuse whole blood platelets, and if so, how has your whole blood platelet use been affected by the new standard 5.1.5.1.1, which basically says if you are using these you have to test.

We had 196 transfusion services respond. A small number, given the number there are in the entire country. About half of them had been users of whole blood derived platelets. And amongst that half, more than 50 percent said well when that standard came out we stopped using these platelets. In other words, they switched to apheresis or pre-pooled platelets.

So certainly there are a number of hospitals -- an unexpected, I think, result of AABB requiring the test for whole blood derived platelets was some people saying we don't want to do it, we just won't use whole blood platelets because we are not required to do that for

apheresis platelets. I think it just says you don't really know unless there are no alternatives, you don't know what individual institutions are going to choose.

Now it may be those 98 places, the 50 that discontinued could have put the test in and they may have been very successful, but they made a choice not to do so.

DR. HOLLINGER: The standards that are set, but whether it is apheresis or whole blood, they still need to culture? On the first day?

DR. KLEINMAN: No, for apheresis platelets everybody cultures. But for whole blood derived platelets, culture is kind of impractical because you take too much of the volume from each individual platelet.

DR. HOLLINGER: From a pre-pooled, though?

DR. KLEINMAN: From a pre-pooled they culture. But from the non pre-pooled, like we were hearing from Dr. Yazer, the new standard in 2011 required an FDA licensed test. Meaning, at that time only the Verax test.

DR. KUEHNERT: Just getting to some specifics, what bothers me a little bit here with the questions is that right now there is a wide range of practice as far as what is being done. Yes, apheresis units are cultured. But there are different ways in which it is done. And then there are these point of use tests, in terms of what is being tested in the hospital.

But I am a little bothered by the options. I think when we get to that, everyone is going to have a little bit of a different opinion on what should be done and it is going to be hard to force everyone into one of these choices. I wonder if there is an ability to make a comment on other options.

For instance, I think on day one there should be a consideration to increase the culture volume. We have heard from that about proportional volume. But what about the idea of using two bottles? Concerning repeat testing, I think we have seen enough about there being residual risk. Even if there are two bottles being used, there will still be residual risk.

And on this repeat testing, is it feasible to have something done on the day of release, which could be either culture or a point of use test? In other words, not force people to pick one, or to have the entire country use one or the other, but allow there to be variability depending on how the hospital is set up.

So that is just something that I would see, can we consider that as an option to recommend. I have been reviewing these options that will come up in the questions. I am not sure I would vote for any of the above, and would rather go with something else that allows some flexibility

and yet creates boundaries for better testing on Day 1 and repeat testing.

DR. HOLLINGER: I think the issue is, as I look at it, they want us to discuss these options. And based upon what we have heard, what might be a reasonable approach or approaches to doing this? And the only question they are asking, as I understand it, is question one. That's the only question. The rest of it is all, please discuss.

DR. KUEHNERT: One other thing. The other thing I didn't mention about our data is that every single patient that had one of these reactions was immunosuppressed and they had a malignancy. I am wondering if that can be taken into consideration for clinicians. People don't read labels, as far as product warnings. So I don't know if I am going to suggest that. But something to make people aware, particularly if they go to seven day platelets, that one, the product may not be as good as far as efficacy.

But also, there is a sequentially higher risk, the longer that a platelet is stored. And, patients who are immunosuppressed are most likely to have severe complications due to that risk.

DR. EPSTEIN: I just wanted to clarify. In putting options on the table for discussion, we weren't

implying that they are mutually exclusive. So we do envision the possibility that for equally valid alternatives, blood centers might be able to exercise options. That is one point.

A second point is that there are really two strata to the conversation. What can the blood collection center do? What in addition should the hospital do? There is room for improvement in both domains, and we recognize that, and we certainly are open.

Also, just at the very end, there is the question of other. So you are free to propose anything you want. But really the question is, are the interventions sufficiently validated that they could be recommended by the FDA? That is really what we are asking the committee to consider.

I want to make just one more point, because it has come up numerous times in today's discussion. This is about seven day platelets. The seven day platelets that we are talking about are not the platelets you are using now at five days. They are platelets stored in a different container that has a different impact on their quality at seven days.

So we are not saying take today's five-day platelet and use it at Day 7. These would be platelets stored in a different system.

DR. HOLLINGER: Can you amplify on that a minute? What do you mean? A different bag?

DR. EPSTEIN: Yes, it is a different bag. And that has to do with different gas permeability, different ratios of volume.

DR. HOLLINGER: I just wanted the committee to know the issues.

DR. RHEE: If there is a different bag that affects the seven day platelets, it would be nice if I got that information before I could vote on it.

DR. ALVING: I was going to mention something. So I am sure as we are sitting here with our little bubbles above our head about is it four days, is it five days, the FDA is generations ahead of us and you are really thinking what you are going to be doing down the road. And so that is useful information in that we are focusing on four days or five days, if you will, knowing that if you are in a seven-day bag you are going to be seeking other thoughts and other guidance.

And I think knowing that there is the flexibility, it is basically, I really like the American Red Cross approach of, okay, so you test on Day 1, you are covered up to Day 3, you test on Day 3 you are covered four and five, and then let the FDA worry about Day 7. And that

will be a next generation of thought and lots of hours around the table.

DR. METZEL: Peyton Metzel, Fenwal. The container that we used for the PASSPORT study, which was a seven-day platelet, is a seven-day validated storage container. So I don't know of another container that we would be developing, unless since we have been bought by Fresenius maybe that is going on and I don't know about it.

The second thing around five, six and seven day platelets, I am really kind of disappointed that that even got interjected here, because it has really diverted the whole conversation about one question. And that question is the following. If you were in the hospital and you were watching a platelet being infused in a loved one, would you like that platelet to have been tested closer to the time that it is being transfused?

DR. KLEINMAN: I just wanted to clarify a point of information after what Matt said about immunosuppressed patients. The epidemiology of platelet transfusion in the US is not really well described if you go to the literature. However, if you look you can find some information.

And I think it is probably accurate to say that at least two-thirds of our platelet transfusions go to people who are either stem cell transplant patients,

whether they are allogeneic or autologous, or another type of hem/onc patient under therapy. So I think we should regard at least two-thirds of the platelet recipients as being immunosuppressed.

So for practical purposes I don't think you would separate out a platelet going to an immunosuppressed patient versus one going to a trauma patient. You would just assume that there is a good chance every platelet could go to an immunosuppressed patient.

DR. GILCHER: I think we have to heed what Dr. Bianco said. And that is, no matter how much testing and how frequently we do the testing, we will never bring the risk to zero. And what I want to add here is, the question says are there additional measures that may be necessary. And something that we have not addressed today and maybe we don't need to, but we should think about it, and that is, is there anything that can be done to suppress growth in the storage bag specifically, such as something in terms of an additive solution or whatever, that in addition to testing would drive the risk down?

DR. HOLLINGER: And I think that is an important thing, and I think it probably comes down to an area. But it is critical and I think we should discuss that too, Ron. So I want to put the first question to a vote here. And then we will move down and discuss these other things that

have been talked about today including the options, and so on.

So the question is pretty straightforward. Does the committee find that additional measures, any additional measures, pre or post, are necessary to decrease a current risk of transfusion of bacterially contaminated products from the thing that you have listened to today? And so I would like the committee to vote on that. You have got the blinking lights. They are always the same thing, plus for yes, zero for abstain, and minus for no. So let's vote.

(Electronic vote –- 18 for, none opposed)

LCDR EMERY: The Committee has voted and it has been approved with a majority. There are 18 yeses, there are zero no's, and zero abstentions. Once again, I will have to read for the record everyone's vote. Dr. Hollinger, yes. Dr. Bonilla, yes. Dr. Demetriades, yes. Dr. DiMichele, yes. Dr. Gilcher, yes. Dr. Key, yes. Dr. Kuehnert, yes. Dr. Troxel, yes. Dr. Linden, yes. Dr. Maguire, yes. Dr. Pipe, yes. Dr. Rhee, yes. Karen Anderson is not voting. Mr. Cory Dubin, yes. Dr. Schexneider, yes. Dr. Alving, yes. Dr. Becker, yes. Dr. Roseff, yes. Dr. Stroncek, yes.

DR. HOLLINGER: And Celso, how would you cast your vote?

DR. BIANCO: I would have voted yes. But with a qualification that do we have the appropriate tools to do that at the present time that will yield --

DR. HOLLINGER: It is either a plus or a minus here, Celso.

DR. BIANCO: Got it.

DR. HOLLINGER: Thank you. Now let's discuss some of these things. And maybe the first one we should discuss, from what you have heard and from the blood banking and collection centers and so on about whether one should reduce the shelf life from five days to four days. That is, I think, a reasonable thing to ask and get rid of right away, at least from my opinion. Is there any feeling that somebody feels that that should be done? Any comments? We are not voting on it. We should, maybe. Do you want to vote on that? Okay. We will vote.

Should there be a reduction in platelet product shelf life from five to four days? I guess that is really the question. And early culture?

DR. KUEHNERT: I may have problems with this. It is like this combination question. If it were just reduce it from five to four days, I know how I would answer. But now it is saying with early culture. So this is just reducing from five to four days with the current systems in place?

DR. HOLLINGER: System in place. Would you vote to reduce the shelf life from five to four days?

DR. EPSTEIN: I just want to clarify that what we are saying here is in the absence of any other intervention do we think that a reduction in dating would be a sufficient safety measure? And this includes the Day 1 culture.

DR. HOLLINGER: Okay. That is the question, so let's vote on that.

DR. STRONCEK: What was the question? The question was to reduce it from five days to four days, right?

DR. KUEHNERT: No, the question was, if the platelet life is reduced to four days would no other testing have to be done?

PARTICIPANT: Would no other intervention be needed. That is the way I took the question. Just go from five to four and done.

DR. HOLLINGER: Or should it be done? Mine is no.

(Electronic vote – 2 in favor, 16 opposed)

LCDR EMERY: There are two yeses, zero abstentions, and 16 no's. I will read for the record.

DR. HOLLINGER: I changed that. I had it wrong. I am no.

LCDR EMERY: The way it is -- Dr. Hollinger, yes. Dr. Bonilla, no. Dr. Demetriades, no. Dr. DiMichele, no. Dr. Gilcher, no. Dr. Key, no. Dr. Kuehnert, no. Dr. Linden, no. Dr. Troxel, no. Dr. Maguire, no. Dr. Pipe, no. Dr. Rhee, no. Mr. Dubin, yes. Dr. Schexneider, no. Dr. Alving, no. Dr. Becker, no. Dr. Roseff, no. Dr. Stroncek, no.

MR. DUBIN: I am just curious about the lock in. This is on the record and not getting the question right means I am stuck? This goes on the record.

LCDR EMERY: It goes on the record. We can re-vote.

MR. DUBIN: I don’t want to mess up the whole committee. Brian, I was up dealing with a muscle cramp and I didn’t get it right.

DR. HOLLINGER: And I had a muscle cramp too, but it was up here. Let’s revote.

MR. DUBIN: I want to get it correct. People look at that, and I don’t want to answer something I don’t believe.

(Electronic vote – none in favor, 18 opposed)

LCDR EMERY: With the revote, committee has voted 18 no’s, zero abstentions, and no yeses. Once again, for the record I will read it. Dr. Hollinger, no. Dr. Bonilla, no. Dr. Demetriades, no. Dr. DiMichele, no. Dr.

Gilcher, no. Dr. Key, no. Dr. Kuehnert, no. Dr. Linden, no. Dr. Troxel, no. Dr. Maguire, no. Dr. Pipe, no. Dr. Rhee, no. Mr. Dubin, no. Dr. Schexneider, no. Dr. Alving, no. Dr. Becker, no. Dr. Roseff, no. Dr. Stroncek, no.

DR. HOLLINGER: And Celso?

DR. BIANCO: No.

DR. HOLLINGER: So again, discussion about these different options and what the thoughts are and what seems to be reasonable approaches based upon the information that you heard going forward. Yes, Susan?

DR. ROSEFF: I really think some of the discussions that we have had about letting the end user really understand what the risks are, are very important. In the bacterial contaminations that we have had in our institution, we had some very smart people. Sometimes they didn't think of the product, but they thought there was sepsis, who treated very rapidly and the patients did fine.

So I think it is really essential. When I talk to people about fevers it is interesting. The nurses are more concerned than the doctors. And the nurses will call us to say the doctor refuses to report a transfusion reaction. And I say, I will initiate one for you. Can you send me the product?

So if there is any way the FDA can send a warning letter, to send some kind of notification, at least let's start the awareness at the user end level, and have everyone understand the same risks that we understand.

DR. HOLLINGER: Yes, I think that is really clear. Just before I came here, I talked to some of my colleagues in the liver center. These are people who work in the hospital, take care of liver transplant patients all the time. And I told them one of the things we are going to be discussing here is bacterial contamination of platelets. And they had very little understanding of this at all. They were surprised, and listened about what the risks are and so on. So I will just support that.

DR. ALVING: That gives me an idea. It reminds me of the checklist manifesto by Atul Gawande. And maybe the nurses should be really the ones empowered to report these, because they are the ones who are called for the fever. Meantime, the doc is out admitting new patients or making rounds or whatever.

So maybe if it could be more of a team effort and an empowerment, and a lot of the docs, they are going to be rotating from one service to the other, the nurses are there.

DR. HOLLINGER: Good thought, yes. Dr. Becker?

DR. BECKER: The Joint Commission has in the requirements that when there is a transfusion reaction, it is supposed to be reported to the physician and to the blood bank. And I absolutely depend on that report that the nurse makes to the blood bank to tell me about what is going on. Because you are right, I don't hear about it from the doctors.

DR. STRONCEK: We heard a lot of discussion that a lot of people feel that there needs to be more of something done to encourage hospitals to invest in rapid retesting. Yet none of these questions really address that. Maybe the FDA, is there enough on the package labeling and things that nobody needs that? Or should we address a question? Should this committee rephrase a question about how we feel about the rapid testing, if it should be more common or required or encouraged?

DR. KUEHNERT: I think the issue here is that, unlike with viral testing, there is no FDA guidance on this, is that right? Right now. So we are sort of in -- I know there are AABB standards, but in terms of FDA regulation, people are doing what they feel like they need to do. And that is true on Day 1 for blood centers. That is true for hospitals.

And so to me, it just seems like, again, there needs to be some parameters for Day 1, and then there needs

to be some parameters for repeat testing. So I am all for that, but the details are the problem. The devil is in the details, so to speak. So that is where I am having difficulty. And these are sort of good starts here, but none of them encapsulates everything that I would like to see.

Agenda Item: Questions for the Committee

DR. HOLLINGER: So a couple of questions would be, I guess, in the committee I would like to hear you discuss it, along with what you said. Is it important to do some form of testing and at what time, three days or four days, rapid testing or culture, and it seems like the AABB and others will be able to decide what they want to do without saying you are going to do a rapid test or you are going to be doing culture.

I don't think that is the issue so much. The question is, should there be something else done at some point? And then maybe we should discuss at what point, whether it is three days or four days or later, and how should it be done. So what does the committee feel from what you have heard?

DR. PIPE: Specifically to that point, I would feel strongly that we should have something on the record of whether we all think there should be testing at the infusing institution beyond the Day 1 testing. We could

have further discussion about the timing for that. But I would want to leave here having at least been able to offer an opinion about whether there should be additional testing at the infusing site.

DR. RHEE: In that regard, I think whoever has the platelets on whatever day we decide it needs to be tested, should test it. I don't know if it necessarily should be the infusion site that does the testing itself. If whoever is holding the blood at Day 4 tests it and it is clean, then it is clean. What I am looking at, just looking ahead to the question, I am not happy with any of those, so I have an issue.

Basically number four kind of throws everything as an open ended question and says, please discuss what we should do. So I think that the specifics about Day 3 or Day 4, I would rather let the experts kind of make that decision themselves. But as a committee I think we should probably just say we should test, because there is a rise in potential for bacterial contamination around Day 3 or Day 4. I think that portion of it, we will go back and forth for too long and we will argue about that, and we are not really all pros at that.

DR. BIANCO: There is one issue that we need a little bit of help from FDA. Those tests area cleared as quality control tests. They are not cleared like as a

release test, that is, a test that you do and then you qualify the product, like an HIV or a Hepatitis B test. So I would like FDA to address this difference and help us understand how this would be mandated.

DR. HADDAD: The tests that are currently on the market as quality control tests, when we initially cleared them we did not have the clinical sensitivity information on them. But nevertheless, we thought that it was in the public health to have them on the market as quality control tests. So there would be quality control on the process, and there would be kind of continuity tests to examine the bacterial contamination rate and to see if there is any variability in the detection rate.

And we would have been happy to have the information on the clinical sensitivity, to put it in the labeling, so that the relative safety of the use of the product would be known. But the manufacturers never came back to FDA to re-label their products. And obviously we cannot re-label the product unless the manufacturers come to us.

However, now these tests are being used as 100 percent QC. They are being used de facto as a release test. So for us, 100 percent QC is synonymous to release. So in fact that is no longer an issue, whether they are QC or release. They are being used as release tests.

DR. BECKER: I have a quick question, a follow up to what you just said. If something is now labeled or used as a release test, and you don't use it, is there a problem?

DR. EPSTEIN: If and when FDA recommends routine use of a test on day of issue or point of issue, de facto it will become a standard. And we can talk about what is voluntary, what is mandatory. But it would become an FDA expectation, which we may interpret as GMP. So de facto it becomes a release test when we recommend its routine use. Whether it continues to be labeled as a QC test or not, if we have recommended its use routinely, that is to say, on each unit, it becomes a release test.

DR. HOLLINGER: And Jay, while you are still there, the tests, particularly the PGD test for example, is it labeled? Is it in the insert that it has to be done within four hours of transfusion? Or can he do it for a day before?

DR. EPSTEIN: It is currently labeled for testing on the day of transfusion. Which means that it could have been a 24 hour old test. It is usually going to be something somewhat less than that, but that is allowed on label. That is a whole other point, that there has been a lot of off-label use of the approved products. That has

been noted here with the variability of practice. But still, the on label use allows day of transfusion.

DR. DI MICHELE: Thank you for clarifying that, Jay. I think one of the things that I heard from actually the hospital side as well as from the patient side, was that there may need to be some teeth in whatever is done from a federal regulatory standpoint, that would first of all make it mandatory in such a way that hospitals would need to implement this. And hopefully give hospitals and hospital blood banks the staff they need to do this in addition to everything else they have to do. Because it sounds like it is a problem.

DR. EPSTEIN: You know, FDA doesn't redirect the resources in the medical system. But why we are here discussing the issue today is because we as FDA are considering acting. And what we are trying to make sure is that we get the science right. And that is why we are asking you about the sufficiency of the various options that have been put on the table, as well as the other options that have been brought up today.

DR. KUEHNERT: I was going to say a quick thing. You are talking about resources. There is another agency in the government that does resources. And I think one of their never events is a transfusion of an incompatible blood type. And one could consider also an untested unit

at point of release that causes sepsis as being something that should not be reimbursed. But of course, that is not up to CDC or FDA. That is up to another agency. But it is just a consideration.

DR. ROSEFF: I just want to make the point that the resources will not be changed. This discussion will not increase our ability to get more staff or more money. But again, we are not here to talk about staffing or money. But we have to do this within the confines. There have been lots of things that have been added and we don't get more resources or more staff. So not even talking about that.

I really believe that we should do more. But I still don't feel comfortable that the more that we should do is really what I can do. So I get concerned about that. I think that we should not forget that there are, again, other risks that we are going to introduce, when the same people are doing all these tests, that now we in our hospital, as Larry said, we have days we take apheresis and we split it in four.

Does that unit work? Who knows. But there will be a day when, again, the perfect storm happens and we don't have a unit because we have thrown out, or again, we had to outdate faster. And there will be someone, someone

will get up and talk about the death that occurred to their loved one because we couldn't provide them with a product.

So how I see this is, there are things that we haven't yet analyzed. And AABB statements that we have to stop and think about what we are doing and really be very, I guess, data oriented in assessing what we are going to do. So we do not have a standard on how big the inoculums should be. We do not have a standard of how long that platelet sits before it gets released, how long that culture sits.

In addition, we have not yet disseminated this information, maybe, as widely as we would like about what the risks are. So if you have a patient who is a hematology patient who is immunologically compromised, and you don't understand that when that person has a fever you need to do something fast, I think all of those things, if they were put into place as we start to look at other alternatives.

I am so happy to hear Verax has another generation. Immunetics is out now. We haven't been able to evaluate those. Those options may work very well, but we don't know that yet. So I would like to think about this as moving toward what we were going to go as a beginning, to implement some of these other steps, and then keep pushing.

DR. SCHEXNEIDER: One of the options that we have not quite gotten to yet is option D, which is the per personal volume sampling which Matt commented on. I find the Poisson model to be somewhat compelling as a way that we could increase safety up front at the collection center without the additional burden in either personnel or financial resources with additional testing.

And if we find the other options to be unworkable or untenable, this is something that could be implemented fairly quickly and may have very beneficial effect.

DR. DI MICHELE: So to the point that is being discussed, that was one of the thoughts that I was having, whether we need to actually get more data. And whether, before the FDA acted in a very definitive way, whether this could actually be examined in ways that the blood centers and all the blood systems in the United States have done so well in the past, and that is to really collect data in a very well-defined way.

It seems like, again, we are going to get to this question. It seems like are there things that can be done in the upfront culture? The issue of the inoculums and whether proportional sample really needs to be implemented. You could think of a two-arm trial in which that was done, going into another two-arm trial about how best to do point

of release testing, whether it be by culture or by rapid methodology later on.

And maybe, for those individuals who may need more data to really justify the implementation, this might be another, more evidence-based way of doing it. And I seem to have gotten the impression, from some of the larger collection agencies, that this is something that they might be willing to do, and certainly might be willing to provide some data on.

So it is something I think the committee should consider. I was going to bring it up in D, but obviously everything is kind of getting mixed.

DR. BENJAMIN: If I could address this -- Dr. Richard Benjamin, American Red Cross. We in fact have published some data on this, Dr. Anne Eder and myself, and the Red Cross published, when we moved from four to eight mls on the BacT/ALERT, and showed that our pick-up rate went from about 140 per million to about 210 per million.

So we saw about a 50 percent increase in pick-up, in doubling the volume. And we published this five years ago, along with the Poisson analysis of going to 60 and 20 mls, et cetera. It has become popular again recently. But we considered that. And we have considered it today. Unlike some other blood centers, the cost is actually quite

considerable today. It is about $8 to $20 per distributed product for us to move to increased volume.

The concern I have is that it is a bit of a distraction for two reasons. One, the Irish study has already done the experiment. When they do proportional volume and so does the United Kingdom today, they do 15 or 16 mls per split unit. So a triple will get 48 mls tested. And they have also showed quite dramatically that outdate testing shows that they only pick up 20 or 30 percent using that enhanced testing model.

So this is I think an important step forward. But we are only going to get to 200 to 300 per million when we know that the actual contamination rate is somewhere like 1,000 per million according to the outdate studies. And so it is an incremental increase that does not necessarily guarantee safety out to day four, five, six or seven in my view.

There is a cost. It is an incremental improvement, 16 mls, 48 mls, a large part of that cost is a decrease in split rates that we get. And so that is an important thing, decreased availability of blood. So there are pros and cons to this. It is not the whole answer. We are still going to need day of transfusion testing, or reculture, or something else. We can’t get the Day 1 cultures, is my view.

DR. DI MICHELE: And I certainly wasn't implying that. I was just looking at steps along the way, including Day 3, 4 testing. So no way was I implying that is the only intervention.

DR. KLEINMAN: Just a couple more pieces of information. Ninety percent of the apheresis supply is tested by the BacT/ALERT in this country. But the other 10 percent is tested by the Pall eBDS system, which is a different system. And I think it would be of interest to note that that system only inoculates -- it was mentioned this morning -- three to four ml of product. It may have equivalent sensitivity. Nobody has really measured it. Analytically it does. It still detects down to one CFU per ml.

But people who use that system are inoculating half the volume of the majority of BacT/ALERT users who we have heard are using eight mls. And as we have heard from one of these speakers in the open session, she works at a blood center that is still using BacT/ALERT and inoculating only four mls. So we do have a difference in practice currently, even without going to volumes above eight ml.

And now we have an even greater difference of practice, because we hear that Blood Systems is going on their doubles to 19 mls. So there is a wide range of culture practices, and I guess that is just the point I

wanted to make, so you could have that when you talk about what should happen next.

DR. HOLLINGER: Steve, just a question. Do all blood collection agencies use diversion pouches? Is that a requirement.

DR. KLEINMAN: It is an AABB standard. And I think almost all people who collect blood, or centers who collect blood, are AABB members, but you don't have to be. And so there could be centers who are not AABB members. They might use diversion pouches anyway. But they would be under no requirement to do so. I would assume that is fairly standard.

DR. RHEE: If we are talking about the volume for the culture, I have a question regarding that, which is, there is not a lot of volume that we are talking about. So when we go from eight to 16, what percentage increase is that in wastage?

DR. TOMASULO: The dose of platelets transfused with the higher volumes is exactly the same. We either collect more and then take it out by decreasing the split rate, as Dr. Benjamin said. So this is completely transparent to the patients. They are getting the same dose of platelets.

DR. KUEHNERT: Peter, can I ask you a quick question? I didn't get to read your article all the way

through so maybe you can answer this for me. I am sorry if it is in there. But you showed that proportional volume helps. But did you show that for that particular volume, that increasing the volume doesn't help given a certain volume?

DR. TOMASULO: Actually, the model just tests increasing the volume. And so when we say proportionate, it is important in the US, where there is aggressive use of apheresis devices, to split platelets. So that in the past, we do all our cultures from the mother bank. A single, there is 247 mls average over a year, 247 mls in a single bag. And it is different for different devices, but just bear with me.

And we put 8 mls in a culture bottle. Nearly 500 mls in a double. We put 8 mls in a culture bottle. Between 600 and 700 mls in a triple. We put 8 mls in a culture bottle. So that didn't make any sense to me. And then when Steve Wagner taught me how to analyze this it became apparent that we ought to be putting the same proportion in if we wanted to really capture what we could be capturing.

And when we did the analysis and assumed that the level of contamination was below that 60 number, we are on the steep slope of the curve and we see increased pickups.

DR. KUEHNERT: But what I am asking is, I am just going to stick to the point because I think it is really important -- you are assuming that the 8 ml for the single is the optimum, right? Or was there some modeling that you did to show that 3.8 percent --

DR. TOMASULO: No, there was no modeling to pick the 3.8 percent.

DR. KUEHNERT: Because it could be higher. The optimal volume could be higher, right?

DR. TOMASULO: Sure. And in fact, if you look at the literature, Dr. Murphy is about five percent, and the Colindale Centre in the UK is about six or 6.5 percent. And we don't know what the starting levels of contamination are. We don't really have any way to compare what is going on across borders. But I am not saying that we have chosen the absolute right percent. It is a lot better than what we were doing before, is what I am hoping to show.

So the bottles are limited to 10 mls of an inoculum. So that is why we said 9.5. You try to get as much as you can into the bottle. We use two bottles for doubles. And because we participated in the PASSPORT study, we have the incubators. And for the triples right now we are only doing 2.8 percent for the triples, because we want a bigger collection device to take the 25 mls that

will be required. And then we will put that into three bottles.

DR. KUEHNERT: All aerobic bottles?

DR. TOMASULO: Yes, we are going to go all aerobic to start with. But look at our data and see what we pick up and see what it means.

DR. DI MICHELE: Actually I could ask a question of both of you, since you are both standing there. Because both of you have looked at this issue of increased volume on Day 1 testing. But maybe I have missed it in the amount of data that we have seen. But has anybody actually looked at that difference in Day 1 testing on what you find on Day 4 testing, or Day 3 testing, for those of you that are doing it?

Has anybody actually looked at the effect of the volume of Day 1 testing on Day 4 testing? Because that is what I was envisioning, and I didn't think there was data for that, and that is what I was envisioning in the schema that I was proposing.

DR. BENJAMIN: I do have some data that addressed it, not quite in the way that you suggested. We have patient data and sepsis data in our haemovigilance system. We have looked at the rate of sepsis for units that originate from a single unit, a double unit, and a triple unit. There is no statistical nor even trained difference

in the rate of septic reactions per transfusion, in products that are coming from a single, a double, or a triple unit.

Having said that, this will be represented at the AABB by Dr. Eder, Anne Eder, as a plenary presentation next month. Having said that, because we have three units out of a triple, and three opportunities to find sepsis, in fact the rate of sepsis is higher for triple collection. But the per transfusion rate is no difference, despite the difference in volumes of collection and the ratio of sample to product at the beginning.

So that we took as really good news. We looked at that hard. They are statistically valid, and there are no differences at this point of time in sepsis.

DR. TOMASULO: Two other points on that question. One is, on one of my slides I tried to -- and I know this comparison is not rigorous, but I looked at the 10,000 cultures that were done in the Fenwal-Jacobs study, and the 10,000 cultures or 12,000 cultures that were done in the last two years in Ireland. We don't know for sure what the volumes inoculated in Dr. Jacobs' study are, but they were probably eight mls. And they were probably taken at 24 hours.

He found five positive, using a microplate culture technique. Dr. Murphy for the past two years

hasn’t found any positive apheresis platelets in a similar number. I am not suggesting that is a valid comparison or that it really says these are the right numbers. But there is something there, I think.

The other point is that the way a platelet gets contaminated isn’t very clear. That is, if you imagine that there are a bunch of bugs on your skin and it is on a skin plug and it goes into the bag, then it wouldn’t make any difference what the volume in the bag was, in terms of the number of bugs that ended up in the bag.

But, if the donor is bacteremic, the more blood you take, the more bugs there would be in the bag. And that would influence the rate of positivity on singles, doubles and triples. So it is a difficult analysis to do, what is the risk. And so we just focused on volume.

DR. BENJAMIN: I will just comment that I agree with Peter that increasing the sampling of doubles and triples will definitely make things incrementally safer. It just won’t make them safe.

DR. BECKER: I am going to completely change things. I am going to go back to Dr. Gilcher’s comment about is there something we could add to the bag. I am at an oncology hospital, and that is all I see. And looking at the white counts of the patients who get transfused with platelets at my institution, 70 plus percent of them have

an ANC of less than 1,000. These patients by protocol are getting broad spectrum antibiotics.

It leaves the obvious question to the other 24 percent. Do I do what our surgeons do when they are starting surgery, and just give them a dose of broad spectrum antibiotics?

DR. KUEHNERT: It is not going to help you if there is endotoxin, though.

DR. BECKER: It might help with the gram positives, but it won't go anything for the gram negs.

DR. RHEE: Yes, but you can't do that. That is a completely different scope than what we are going to talk about today, if we are going to start discussing what we are going to invent to put in these things. Because you will kill people with the antibiotics, one out of 1 million, in things like that, too.

DR. WAGNER: We had considered in the early nineties about adding antibiotics to the bag and did some studies where we added gentamicin, which seemed to work pretty well. But the problem is just what was said. A certain percentage of people are going to have anaphylactic reactions to the antibiotic. And you may end up doing more harm than preventing the cases.

And so when you are a physician at a hospital, you perhaps know your patients a bit better. You know what

the antibiotic sensitivities might be. You can select something that is appropriate. You really don't have that knowledge when you are working at a blood center about what to add to a bag.

DR. DEMETRIADES: Mr. Chairman, just for your information, there are ongoing studies using ultraviolet light to sterilize blood. So maybe in the near future we will see some advances.

DR. STRONCEK: My preference to deal with the bacteria contamination issue would be pathogen inactivation. But I suspect that has been the topic of this committee on other occasions, and it is a whole two or three day discussion.

DR. KUEHNERT: It looks like Jay is getting up so I was going to just see if FDA needs specific advice on the options, or whether you want more comment about what each member thinks should happen.

DR. HOLLINGER: I am just interested in the group here, how many people here think that there might be some benefit of extending the time to seven days. Assuming that you are going to add something somewhere in there, a second testing, which I think would be appropriate if you are going to extend it. Anybody that is terribly against that?

DR. ROSEFF: I don't think it is going to help. We have a very, very low outdate, very low. So I don't

think it is going to help us considerably. It will help us a little but I don't think it will be considerable.

DR. HOLLINGER: So it is not an issue for you, okay.

DR. KUEHNERT: I think when some of this testing comes into play it is going to delay the platelet release somewhat in the hospital. And if you have got problems already, you are going to need a little extra time. So to me, I think seven day storage should be considered.

DR. HOLLINGER: Some of the data that was presented suggests that some of the risk comes, continued risk is at the fourth and fifth day. And so the question is, at what point do you think that there should be some testing done? At the third day?

DR. KUEHNERT: The thing is, before you asked that, I think that one could choose three versus four. Or you could just say on the day of release. Unless I am getting this wrong, that a hospital doesn't know when it is going to be released. But if you anticipate it is going to be released on that day, you could make it three, you could make it four, five, six, seven.

DR. BIANCO: During the PASSPORT Study, I don't know if Larry is still here, but there was for many of the centers there was substantial help in terms of having inventory of platelets on Tuesdays, Mondays and Tuesdays.

Because they could stretch the collection dates and increase availability. So it was very helpful.

DR. EPSTEIN: On this point, I think we have to dissociate two issues. We have already approved certain platelet collection containers for seven days, based on the standards that we apply for the safety and efficacy of the platelets. The reason we are not exercising that option is bacterial contamination. Because we know that the rates of significant contamination go up with the duration of storage, unless we fix that problem.

So to a certain extent we don't need to debate whether there should be seven day dating. If we have resolved the risk of bacterial contamination we have systems that permit seven day platelets.

DR. HOLLINGER: Just to be sure, that means, though, that you would have to use the particular bag you are talking about, from the very beginning, right?

DR. EPSTEIN: Correct. In terms of what more we would like to see from the committee, I think it would be helpful if the committee were willing to vote on option three, because that is the one that focuses on whether there ought to be additional repeat testing on the day of issue. And the way it is framed, it would be simply the day of issue. That would include Day 3, Day 4, Day 5, Day 6, Day 7.

Now we have framed it for Day 5 because we were basically looking at enhancements to the current system. But I think it would be helpful, given the broad discussion, if we could at least get clarity on that point.

DR. BIANCO: A request to Dr. Epstein. If the question requires only culture or if a rapid test could be included.

DR. EPSTEIN: I'm sorry. I am talking not about C, but question three. You have to scroll down. That is the one.

DR. HOLLINGER: But three, you are talking about retesting with a rapid test rather than a culture.

DR. EPSTEIN: The way we proposed it earlier was sort of either/or. But here what we were saying was, can you qualify Day 7 platelets if you re-culture on Day 4? I think we have heard some data that suggests that that is insufficient. We only heard that today. This was the issue of the sepsis rate on Day 3. So we could revise that and ask whether cultures on Day 3 would qualify Day 5 platelets.

But here we are just asking, not taking culture out of the mix as an alternative, because that is a separate discussion, do we think that we can assure or best assure the safety of platelets out to Day 5 if we do a once a day re-test on day of transfusion?

DR. HOLLINGER: Here you have commented though, I think, in this one -- and correct me if I am wrong, but you are talking about strategy to culture platelets after the first 24 hours. And my understanding is that many cultures are done right away, on Day zero.

DR. EPSTEIN: No. Some facilities are waiting perhaps 18 hours instead of 24. But there is a waiting period for all the cultures. So what we are saying here is, should we consider the alternative, assuming that we follow the advice in question one, that we must do something. Should we consider as a scientifically valid alternative the concept that a rapid test is done on the day of transfusion subsequent to negative culture obtained on the Day 1 stored platelet? Is this a viable option?

DR. KUEHNERT: When you say a viable option, I would rather see a culture. But if you can't do a culture, I think a rapid test is the next best thing. So I don't know how I would vote, given that I feel that way.

DR. HOLLINGER: Well, you have made the opinion clear.

DR. RHEE: I think the culture is better, but from a logistic point of view, that is going to make it very difficult to do. Sometimes you give these products on Day 3. And I would say if you give it on Day 3, the data that was presented to me today says you don't need to do

anything on that one. It starts to go up on a logarithmic scale from Day 4, and then Day 5 is the main issue.

So if you have a product that is going to have to stay till Day 5, I would say test is on Day 4 so that in case you need it on 5, we can just give it, but if you do it just before you give it, that is going to cause a delay. You order platelets and then they are going to have to test it? It is going to take hours to get the order, they are going to test it and you have to wait four hours and all this, yada yada yada. And it is going to be way too late from a clinical standpoint, if you test it right before you get it.

So I would say you are concerned about platelets which grow bacteria, and it goes up under fourth and fifth. It is very small but it is there. And from the data you guys gave and presented, if you do a rapid test you can catch it and reduce it by maybe half. So I would say for products that are there, on Day 4 my opinion is, Day 4 test it. And if it goes out on Day 4, it goes out on Day 3, then you don’t need to test it.

DR. JACOBS: Please look at slide 35. Four of the positive tests that we found by the rapid test were on Day 3. Four of nine. That is almost 50 percent.

PARTICIPANT: But you had your other three misses on Day 5, your false negatives, were all transfused on Day 5.

DR. JACOBS: But they were only tested on Day 5. But we had four on Day 3, which were already reached those high numbers.

DR. KUEHNERT: I would agree. I think you are going to catch a lot of them on Day 4, but Day 3 also, there is a risk.

DR. BIANCO: May I just remind all that what you are proposing is that all platelets be tested by the PGD or the BacTx test before release, because it is Day 3, Day 4, Day 5. You just added a test to every single unit of platelet that is leaving the center.

DR. HOLLINGER: That's right. The way this is written is that you test it at 24 hours, but that sounds like just before transfusing, whether it is Day 2, 3, 4, or 5, you would do a rapid test.

DR. YOMTOVIAN: May I make a very brief comment? So with this alternative one could add, at least if people like it and it is phased in, one could add doing a culture at the time one does the test for release, or near the time of release, for a certain number to at least get a sense of how reliable the rapid test is. Just a thought. And get good data.

DR. HOLLINGER: So Celso, what you were saying on looking here, would you put a time limit on when the second test would be done? That is, if you do culture after the first 24 hours, would you be reluctant then to use a rapid test on the second day or the third day or the fourth day? At what point would you suggest --

DR. BIANCO: The initial thing that was discussed is that the rapid test on Day 4 and 5 would be testing 50 percent already of the platelets that are released, and which is a big burden to these centers. And when you look at the benefit that you would get, it is relative. And if you add Day 3, then you are going to go essentially, because of the 24 hours that most centers, the first day is testing and other things, you inoculate at 24 hours.

Most centers or many centers will release after 48 hours. Then you are already in Day 3. So essentially you would be testing every product with a PGD. And it is a big addition to the system. And I think that we have to think about the benefits that will be derived from that.

MS. CARR-GREER: Moving to focus on this question the way it was worded when it was up on the board, is the committee now focusing just on the product that is currently being cultured at 24 hours because we are no longer looking at the product that AABB certainly had a

concern about when it put into place 5.1.5.1.1, and that was as whole blood derived platelets that are not cultured.

DR. KUEHNERT: I think there is a risk differential between apheresis and pooled platelets. And that does need to be emphasized. So if anything that is the biggest concern. The fact of the matter is, it is only 10 percent of platelet transfusions in the US. So it is sort of put under the rug. But it is a big issue.

DR. HOLLINGER: I am not sure I would agree that you would do a re-test once with a rapid test on every day after the first 24 hours. If you do it at 24 hours the way it is written and you have a culture done and it is negative, but then you administer the platelets on the second day or third day or fourth day, I am not too sure that I think that is necessary. From what I have seen I am not convinced.

And the data has not convinced me. I know that there have been some cultures and so on that have been positive on that Day 3 and Day 4. But I don't know anything about how those bloods were collected. We talked about diversion pouches. Were they done in a center that used diversion pouches. Nothing was told to me about how that was performed, or about how that particular blood was collected and so on.

DR. BIANCO: I must confess that I misread the question, number three. Because the strategy that is being proposed is to culture after the 24 hours of storage, in the first culture that was done. And then re-test just once with a rapid test on the day of transfusion.

DR. HOLLINGER: That means that every transfusion --

DR. BIANCO: Every transfusion that leaves will have to be on Day 3 or Day 4 --

DR. HOLLINGER: Or Day 2.

DR. BIANCO: -- will have to be tested just once, but will have to be tested by the rapid test.

DR. KLEINMAN: I just wanted to follow up on what Allene said, that if the FDA takes a regulatory action, you are debating today the action they should take for apheresis platelets. But the FDA has no regulatory position now on whole blood derived platelets. The AABB has a standard. The FDA has no position. And the FDA has no position on pre-pooled and stored platelets, the so-called acrodose platelets that are generally cultured.

So it would seem to me that if the FDA does decide to take a regulatory position on apheresis platelets, they should not neglect taking a position on the other two types of platelets that are transfused in the US, because it wouldn’t make sense. We regulate this part of

the platelet supply, yes, it is 88 percent, but there is still another 12 percent and they shouldn't leave that just to people's own considerations. So just to remind the committee that we are talking about the most important part of the platelet supply. It is 88 percent. But there is another 12 percent that we need to consider.

DR. KUEHNERT: And a lot of those pooled platelets are collected or transfused at large cancer hospitals. So those are exactly the patients that are going to be the most vulnerable. Although most platelets are given to those types of patients. But that is even more of a predilection.

DR. EPSTEIN: We are aware of that issue, and we would certainly address platelets pooled on the day of issue. We understand that we have to address that. Perhaps the caveat here is, we are talking about either apheresis platelets or acrodose platelets. They are the ones that can be cultured up front.

Now we know that it is theoretically possible to culture single units up front and pool them later, but that is very cost adverse and centers aren't doing that for the most part. It is done, but it is done rarely. Anyway, the point is, we understand Dr. Kleinman and yes, we would have to address whole blood pooled platelets.

DR. ROSEFF: I want to get back to what Celso was saying. We don't know which units we are transfusing on which days. So I guess what we would have to do to comply, on the day of transfusion, and knowing that we can't do it at issue, we are going to have to probably do them, every platelet every day, unless there is an every platelet that is four days or older kind of definition.

And the other thing is, too, that yes I believe we need to do something once. But I would still love to see data on Immunetics' new test, and the upgraded Verax test before I know what I am going to do. So although I think yes, I feel like I don't know how to do this until I get my questions answered, which will take time.

DR. ALVING: We don't have to say yes – what are our options?

DR. PIPE: Isn't that the spirit with which we are answering this question? We are not saying what to do. We are just saying something has to be done. I don't know that we have to decide the options. The FDA can evaluate, and work with other recommendation bodies. But I think personally I don't think Ms. Massari should drive home without us having had an opportunity to say that something is going to be done differently with how platelets are handled from this point forward.

DR. DUBIN: I think I want to underline that and go back to what Dr. Yazer said. That is part of what we have been saying today. I appreciate Dr. Pipe, that you took it the specificity there. There is a lot more of that specificity that we need to speak to, and I would feel much better carrying back a message next week that there was more definitive action recommended to act on this.

And maybe I misspoke my choice of words of lack of will, because my goal isn't to do a look back that is designed to getting anybody's feelings out of whack. It is more to say, if we remember this it is not hard to understand that the folks would be a little uneasy 16 years out, knowing of the complexity, Jay, that you talk about, and that others -- you, Celso. But also understanding how you feel, ma'am -- I forgot your name, I apologize, in the back there, about your daughter. And how I know some of the people on the phone I deal with feel. So I really think this is critical. Thank you.

DR. HOLLINGER: Any other comments?

DR. EPSTEIN: I have the sense that the committee might be more comfortable if we limit this to days four or five, and then separately ask, should the same apply to Day 3. If that makes sense to the committee members, we can just modify the question accordingly.

DR. KUEHNERT: Sorry, you are going to have to simplify it for me. So what if I feel it should be on the day of release? Regardless of the day, then how would I vote?

DR. EPSTEIN: You would vote yes twice. You would vote yes to Day 4 and Day 5, and then we say should the same apply to platelets released on Day 3, and then you would vote yes again.

DR. KUEHNERT: And as far as the feelings on Day 7 storage, you said that is not an issue?

DR. EPSTEIN: We are not asking that in this question.

DR. KUEHNERT: The last question I have is, it says rapid test. But for me, I would accept I think a culture is more than acceptable. I wouldn't want to limit it to a rapid test.

DR. EPSTEIN: And again, I think FDA did not see these options as mutually exclusive. We are just trying to figure out among the set of options are there some equivalent alternatives? And we are not taking culture off the table. I am not sure we have gotten quite a consensus opinion on when and how to use follow up culture. We could ask about culture on Day 3, culture on Day 4. It is in the set of options.

DR. RHEE: I have to say something about this, because we have heard some sad stories today and these are all realities, and people get hurt from the medical system as well. But I can't tell you the number of times, it wasn't just once, the number of times where I go to the blood bank and I am screaming and yelling and I am really angry, and we go through weeks and weeks of meetings. The next day and so forth.

And the policies that we have in our hospital about getting blood, getting blood quickly when I need it, right away, and I feel like, you know what, this guy died on the table because I couldn't get my products because of the FDA and because of too much regulation and stuff. Sometimes we have got to get the stuff, and you have got to put things into perspective.

So before we regulate and mandate too many things, I have been in that situation multiple times myself -- I am sure Dr. Demetriades can tell you as well -- where we feel like the regulatory system sometimes is hurting us as well. So I don't think we should mandate too much in the sense as well. We should do what makes sense, what the data shows.

But if you are going to make them do, make sure that every single thing is perfect every time in an unperfect world, you are going to hurt people.

DR. ALVING: I think we have some data, and I think when we saw that really it seemed that the issues were not with Day 1, Day 2 or even Day 3, it is Day 4, Day 5 -- then the American Red Cross has done good studies. And it would seem if you could do, you would say you are covered with Day 1, Day 2 from your culture, and then you would do rapid testing, let's say, on Day 3 and that would cover you presumably for Day 3, 4 and 5, I don't know, how would you ideally do it at the American Red Cross, for example?

DR. BENJAMIN: Thank you for the question. I am in favor of a rapid test on Day 4 and Day 5, clearly. Day 1 and 2 doesn't come into it because no one transfuses on those days. The platelets are getting to the hospital on Day 2. So Day 3 is really the only question. If we mandate a rapid test on Day 4 and Day 5, hospitals are going to ask us to get the platelets to them earlier, right?

So on the afternoon of Day 1 we normally hold, we used to hold for 24 hours, currently we hold for 12 hours. So we release them through inventory the next morning essentially. On a four and five day retest, they are going to say, ship them to us overnight and let us know whether the cultures go positive. So there is some risk in that, but they almost certainly will be asking for that. They

will try and avoid the test as much as they can. Maybe it will do some good because the patients will get fresher platelets. Maybe that is good. But there will be some risk.

Certainly I am in favor of Day 4 and Day 5 retesting, and 6 and 7, because I think there is a need for a longer outdate of platelets. I frankly don't believe there is any data to say that older platelets are bad for patients. They might be slightly less efficacious. But Day 3 I think is an open question for this committee. And the Verax data says that perhaps we should do testing on Day 3, but the clinical sepsis data says that Day 3 is not so bad. Vote your conscience on Day 3, folks.

DR. MURPHY: What I would do based on what I have heard today is, I would do a rapid test with the culture on Day 4 or on the evening of Day 3. The culture is going to be better, and will cover you for Day 5, 6 and 7 I would think. But if you had done a rapid test, the culture must be more sensitive than the rapid test on Day 3. What you are suggesting is that you are getting lag phase bacteria appearing on Day 5, 6 and 7 that aren't there otherwise, that you won't detect with a sensitive 15 ml test. I can't see that your data show otherwise.

DR. BENJAMIN: Absolutely, if we had the platelets in hand we would do that. But the idea of

actually getting the platelets back to the blood center, it takes us 18 hours from release into inventory to actually get them to the hospital, to get them back to retest and back to the hospital. We are talking Day 8, 9 and 10. In the US system, we can't do that.

DR. JACOBS: If I can just add from a practical point of view, for the year that our blood bank was running the tests, they were basically testing our platelets on receipt and then retesting if platelets weren't used the next day. And the retest rate was approximately five percent. So it really doesn't matter what day you test. Although again, this was a large institution. For small institutions this would be different.

DR. HOLLINGER: One of the problems is, there are so many possibilities. We had enough options here. But again, for me, I would not have a problem with testing again on Day 4 or Day 5, and how to get down around Day 3, it would come down to volume again. Using more volume for even a proportional basis for the blood. And I think that would handle that, into Day 4 and Day 5 at the time.

MR. DUBIN: Is there a way that we not get lost in the debate and come to some middle ground so we accomplish something today that we can take out of here?

DR. EPSTEIN: I have reworded the questions for the committee. It is going to be projected in a moment,

but I will read it. Basically what we are saying is, for platelets limited to five days of storage do the available data support a strategy to culture platelets after the first 24 hours of storage and then re-test Day 4 and Day 5 platelets once with a rapid test on the day of transfusion.

And then as a separate question, should the same approach apply to retesting of Day 3 platelets? And I think the committee can probably advise us on those two points.

DR. RHEE: Day 4, Day 5 – that confuses me. Because if you test them on Day 4, I think the data shows it is pretty good that you don't need to test it on Day 5 again on the one you just tested on Day 4. So there is a percentage of the products that don't get used earlier that hang around to Day 5. And I think that was somewhere around 20 percent or so.

So I was thinking, on Day 4 what is still left in the fridge, stuff that is not so good type of thing, that is the one you test. And if they want it the next day you go ahead and give it. But I don't think you should test it the day of infusion, because that is going to delay it. And in my particular field that is going to be a problem.

DR. EPSTEIN: I respect that line of argument. But it overlooks the doubling time. See, the issue is that the rapid tests are less sensitive, far less sensitive than

the culture. So we are screening somewhere at the sensitivity of 10 to the five or 10 to the six. And then if you allow another 24 hours of growth at room temperature, you could have a significant change in titer. That is the argument against that, which would call for then retesting it on Day 5.

DR. RHEE: Some of those things are theoretical. And we've got to look at things in perspective, right? You can't get lost in the trees. You have got to look at some of this in perspective. Look at the overall numbers that you are talking about, number of deaths per year. The number of deaths I have had personally from bacteremia, I don't have any.

I have people who have fevers, sometimes they get it around my transfusions. I don't know for sure whether it was related to one of the many things. I don't work in an office environment. I work in a different environment. But the number of times I have had a patient die on the table from coagulopathy and that I wanted to fix is too many times, it is too numerous to count.

So in comparison, for me, if we make it so that there is a delay and I don't get the products, that person would feel like that is going to hurt me.

DR. SANDERS: If I might offer an interjection. Joe Sanders with Verax. Speaking specifically to the issue

of availability of platelets. Again, we do have about 150 hospitals in the US that run the test on a routine basis. None have reported to us when we specifically inquired. We surveyed 50 of them randomly that they had any availability issues in being able to issue platelets to the floor, because they typically follow a batching process.

They are not running individual doses before they issue them.

DR. RHEE: How many of them do the rapid transfusion protocol? For the rapid transfusion protocol is it a little different thing.

DR. SANDERS: All I know is what they typically do is, they batch it. Sometime that is convenient for them to have units available, when they are most likely to face the demand. And that either means late on third shift or at the very beginning of first shift.

DR. RHEE: Right. That is not in my setting.

DR. SANDERS: And they have units available for transfusion.

DR. RHEE: That is not in my setting. For rapid transfusion protocol, which we are going around the whole country and the world saying that they need to have, because this seems to be a way for us to get products early and timely, and before we have to do individual testing and figure out which component therapy is necessary, we are

going back to the idea of whole blood. And this has saved more lives than any one of us combined.

Yet when we do it in this particular situation it is going to really hurt. That is the only time that really it is going to hurt us overall.

DR. HOLLINGER: I guess what I hear maybe here is how difficult is it to anticipate that the platelets will be used at the time? At what point will they be tested?

DR. BENJAMIN: Can I just comment here that every hospital I have worked at or gone to has an emergency release protocol. If you come to my blood bank and say can I have five platelets, et cetera, now my patient is bleeding out, I turn around and put them in the box and say sign here, good bye. Take them. So everyone has that. For trauma protocols, et cetera. So this situation I think is not real. Every hospital has emergency release protocol. That is what we use. We know about this. If they have to be untested we will send them out untested. And most of them un cross matched even.

DR. RHEE: If you are going to have an asterisk then say so from the beginning, and say for my patients it won't matter.

DR. BENJAMIN: No.

DR. BIANCO: I understand the issue, Dr. Rhee. And if it is emphasized that a test is valid for 24 hours,

which is what is in the packaging cert now, if it is tested on Day 4 you are going to have it valid for at least half a day, on Day 5.

DR. HOLLINGER: And then would it be outdated at that point?

DR. BIANCO: No, you could retest it, if you wanted to release on that day. But you reduce the proportion of units that were there. But it has to be emphasized that FDA will retain these 24 hours, not the question of the four hours.

DR. HOLLINGER: I think we will call for a vote and get through here. I think the FDA has heard something. As I said, I will vote for this but the concern that I have is, again, I think that they could increase the volume at the beginning to drive this past the third day. And you don't have that in there, but you are listening so I think that that will come through. I would like to close this, and go to a vote on what we have here.

Let me read this again. Let's vote. Right on here, it is just one vote.

(Electronic vote – 16 for, one abstention, one opposed)

LCDR EMERY: The Committee has voted and it has been approved with a majority. Sixteen have voted yes,

there is one abstention and one no. I will read for the record the votes.

Dr. Hollinger, yes. Dr. Bonilla, yes. Dr. Demetriades, yes. Dr. DiMichele, yes. Dr. Gilcher, yes. Dr. Key, yes. Dr. Kuehnert, yes. Dr. Linden, yes. Dr. Troxel, yes. Dr. Maguire, yes. Dr. Pipe, yes. Dr. Rhee, abstained. Mr. Dubin, yes. Dr. Schexneider, no. Dr. Alving, yes. Dr. Becker, yes. Dr. Roseff, yes. Dr. Stroncek, yes.

DR. HOLLINGER: Here is the second part. And any comments on this at all? Barbara?

DR. ALVING: What if you just don't know? Can there be more data or something? Or do you just abstain?

DR. HOLLINGER: I am like you. I would abstain on this, just because there are so many other alternatives and issues here that are not brought up in this question.

DR. GILCHER: I want to be sure that we are all understanding the definitions of Day 1, 2 and 3. When does Day 3 begin? What is the understanding of everybody in this room? At what time does Day 3 begin? Does it begin immediately after 48 hours? Or does it begin at T72?

DR. HOLLINGER: That is a good question. For me it would be 72 hours. You draw the blood, 24 hours later is the start of the first day.

DR. GILCHER: Well Day 3 begins one second after T48. But that may not be the way people understand it in this room. I want to be sure that everybody understands, that we are talking the same thing. And I am afraid that we are not. I think Jay needs to clarify this.

DR. EPSTEIN: We mean 72 hours or later. The reason is that we call day of collection, Day zero. So Day 1 starts at 24 hours.

DR. MURPHY: Mr. Chairman, a point of clarification. In my data, Day 1 begins at midnight on the day of the phlebotomy. And the day always changes at midnight. My understanding is that that is the European convention. It is the European convention. Day zero is the day of collection. Day 1 begins at midnight on that day. So when I talk about Day 7 it is midnight of Day 6. It has got nothing to do with the time of collection.

DR. WAGNER: Steve Wagner. And the way I think about this question is that the answer really depends on where you sit. If you sit at the blood center and people were to vote that they don’t want to do testing at Day 3, then all of the customers are going to ask only for Day 3 platelets. They don’t want platelets later than Day 3. And we wouldn’t be able to supply everybody who needs platelets with just Day 3 platelets.

And so from the blood center's perspective, you could have really large consequences. If you are at the hospital and want to avoid testing, then you say thank you, I don't want to test on Day 3. And then we get into that situation.

DR. HOLLINGER: Okay but as Jay said, for the purposes of this discussion here, Day 3 is 72 hours after the blood is drawn. It may not be right or wrong but that is the way he framed it.

DR. LINDEN: My question is, in terms of supporting strategy, are you saying mandating this strategy? Or if you do this it is satisfactory but there might be other approaches also?

DR. EPSTEIN: Our thinking is, it is the latter, not the former. In other words, for example, I think we have heard some data to suggest that a Day 3 culture might qualify a Day 5 platelet. And we have heard data from Ireland that a Day 4 culture appears to qualify a Day 7 platelet. So we do entertain possible alternatives. We are happy to be advised on all of them, but at the moment we are just talking about the use of the rapid test.

DR. HOLLINGER: Just out of interest's sake, in Ireland even though you start at midnight as Day 1, most of your blood for platelets and apheresis is probably drawn when? How many hours before midnight?

DR. MURPHY: It all depends on the unions, really. The last apheresis donor will go on about half six or seven. And will be complete about eight o'clock. So the last apheresis platelet will be prepared about 12 hours before the guys come in the next day and start to collect. But the schedule the sampling so that they sample the late ones late, and the early ones early. So that is how we come to a mean of 17 hours with a minimum of about 14 hours.

DR. HOLLINGER: So do you want to vote on this? Okay, let's vote on it. This is, should the same strategy apply to retesting of Day 3 platelets 72 hours after collection? Let's go ahead and vote.

(Electronic vote – 5 for, 7 abstentions, 5 opposed)

LCDR EMERY: The committee has voted. There are five yeses, seven abstentions, and five no's. And for the record, Dr. Demetriades has left. And for the record, Dr. Hollinger has abstained. Dr. Bonilla, abstained. Dr. DiMichele, abstained. Dr. Gilcher, abstained. Dr. Key is no. Dr. Kuehnert is yes. Dr. Linden is yes. Dr. Troxel, abstained. Dr. Maguire, abstained. Dr. Pipe is yes. Dr. Rhee is no. Mr. Dubin is no. Dr. Schexneider is abstained. Dr. Alving is yes. Dr. Becker is no. Dr. Roseff is no. Dr. Stroncek is yes.

DR. HOLLINGER: So that probably means is it going to be mandated some way or other? Any other? What else do you want us to spend our time on, Jay?

DR. EPSTEIN: I think we have had a good discussion. I would just invite, if there are any members that want to give any final parting words of wisdom. I don't think we need any more votes, or to open up any new options.

DR. HOLLINGER: Anyone want to provide any further comments? Corey?

MR. DUBIN: I want to thank the committee for acting on this issue. We are appreciative and thankful and thanks to the FDA. And thanks to the committee very much.

DR. HOLLINGER: Any other comments? I don't need to remind the committee, unless you really have to leave right away, they do want to have a public discussion about this public workshop on Hydroxyethyl Starch Solutions that they had in September, which I think is a very important issue. We will take a five minute, 10 minute break and then let's come on back. Thank you all.

(Brief recess)

Agenda Item: Update on Public Workshop: Risks and Benefits of Hydroxyethyl Starch Solutions

DR. HOLLINGER: Dr. Jain, tell us about this hydroxyethyl starch problem.

DR. JAIN: I will present the update on the public workshop on risks and benefits of hydroxyethyl starch solutions. This workshop was held on September 6th and 7th, one and one-half day workshop, at Masur Auditorium.

DR. HOLLINGER: Sorry, I am supposed to read this to the group. The FDA is not seeking advice or recommendations from the committee on this topic. The committee may ask questions of the FDA. But if the discussion appears to be veering toward advice or recommendations, we need to stop the discussion and remind us that they are just not seeking advice on the topic. It is just for your edification. Sorry about that, Dr. Jain. Go ahead.

DR. JAIN: So starting from the beginning, this workshop was held on September 6th and 7th, a day and one-half workshop, at the Masur Auditorium at NIH campus in Bethesda. The sponsors of the workshop are Food and Drug Administration, the Department of Defense, NHLBI from NIH. The scope of this workshop was to discuss new and available information on the risks and benefits of the FDA approved hydroxyethyl starch solutions, which are three now -- Hextend, Hespan and Voluven.

The topics included to be discussed at this workshop there -- risks and benefits of available

intravenous resuscitation fluids in the setting of hypovolemia, especially sepsis, trauma with hemorrhage and peri-operative management. The discussion also focused around pathophysiology of hypovolemia, the use of HES solutions in clinical practice and the results of recent clinical studies that were conducted with the different HES solutions.

Details of the discussions were related to, with the possible exception of volume optimization in elective surgery, numerous clinical studies that were published over the past 25 have failed to demonstrate any clear benefits of the HES solutions compared to other available IV resuscitation solutions. Increased risk of bleeding and renal toxicity have been identified with several different HES solutions.

And recently published data from a large, randomized controlled study trial in sepsis showed an increased risk of renal toxicity and mortality at day 90 in patients who received a six percent, 130 by 0.42 HES solution, which is manufactured by B. Braum, and not licensed in the US, when it was compared to the Ringer's Acetate solution. And these findings are published in the New England Journal of Medicine, in the July 12th issue.

The results from another large randomized controlled study conducted in all ICU patients, and it is

called the CHEST study, conducted with the Voluven, which is a product that is licensed in the US, were not available at the time of the workshop. Other studies using different HES solutions were also presented, and they showed similar results for renal toxicity when used in sepsis and traumatic hemorrhagic conditions.

Older studies performed with HES in elective surgery suggested some benefit, but harm was not ruled out because the follow up of these patients was very short, as short as a day or two.

So the conclusions of the panel were, and the majority of the panel has concluded actually that the toxic effects on bleeding and the renal failure constitute a class effect of HES solutions. And it is possible that the toxicity may be increased for higher molecular weight HES and with high level of substitution and with the administration of higher doses.

They also concluded that no new studies with HES are needed to identify further risks in the sepsis and traumatic hemorrhagic populations. However, additional studies in elective surgery patients with long term follow up could be helpful in identifying long term risks and benefits in this patient population.

There is a need for studies to identify accurate methods for early detection and monitoring of hypovolemia

in various medical settings in order to optimize management strategies. There is also a pressing need for basic and translational clinical research to better understand various aspects of the pathogenesis of hypovolemia. And lastly, a need exists to promote education and proper fluid management for both physicians in training and the current practitioners.

So the FDA considerations based on this workshop are that we have taken note of the panel's conclusion and will consider these in the context of our own analysis of the available data on safety and efficacy of the HES solutions. And regulatory actions to raise awareness of the demonstrated toxicity of HES products are also under consideration. Thank you.

DR. HOLLINGER: Questions anyone? Comments? Use? Experience?

DR. PIPE: I am interested in what data was provided and reviewed for the Voluven to have been approved in the outset?

DR. JAIN: The data that was provided was from numerous studies. Some were conducted outside of the US, because this product had already been licensed before its approval in the US in 2007. And in the US, it was a 100 patient, randomized controlled study in the surgical

population. The study was evaluated and the comparative product was another HES solution.

DR. PIPE: So the studies being evaluated here, are they outside of the indication that this was originally approved for?

DR. JAIN: No, they are all in the indications. They are approved for hypovolemia due to any cause. But they are a large, randomized controlled study where the comparative product is another resuscitative fluid and not an HES solution.

DR. PIPE: And the complications that were observed here, particularly the renal toxicity, does that rise to a level to receive a warning?

DR. JAIN: I think they are considering various options of risk communications based on the available data. We haven't finalized that as yet.

MR. DUBIN: Are warning one of those considerations?

DR. JAIN: It could lead to a warning in the package insert if we consider that to rise to that level.

DR. GOLDING: (off mic)

DR. JAIN: So as part of the approval there was a post marketing study that was to be conducted in a sepsis patient population. And this study actually confirmed the findings of renal toxicity. And based on that finding, the

package insert has been updated in the clinical study section and adverse reaction section. But no additional warning has been added so far.

DR. HOLLINGER: Did you say it looked like the molecular weight made a big difference in the renal toxicity. Is that what they found?

DR. JAIN: It is actually a combination of all the higher doses, the molecular weight, and the substitution. It seems like the molecular weight of Hextend and Hespan is 650 compared to Voluven, which is 130. But they differ in substitution. And the doses used are different, too.

However, in Europe, when they used in HES a molecular weight of 200 with a different substitution, they saw similar, too. So yes, it is an hypothesis, but it has not been confirmed because the data, with Hextend and Hespan, it has not been recently studied. What we have is an older data.

DR. RHEE: This study in the New England Journal of Medicine was with Voluven?

DR. JAIN: The one which was done in the sepsis patient population was not with Voluven. It was a different HES solution.

DR. RHEE: But it wasn’t Hespan or Hextend?

DR. JAIN: No. It is a different one which is only licensed outside of the US.

DR. RHEE: But they were comparing it to a crystalloid, which means that the volumes that they used was also different.

DR. JAIN: Yes.

DR. STRONCEK: This is used, the hetastarch is used in patients donating granulocytes, not for volume expansion but to add sediment red cells in the blood cell separators. Was there any discussion? In that setting are there any problems?

DR. JAIN: We are aware of that. But it seems that the volume used in that type of setting is very, very, very small, so it is more related to hypovolemia.

DR. ALVING: How widely is this used? And where is it primarily used? In surgical situations? And is it used all throughout the United States? This has actually been going around for decades, hasn't it? Or is it just me? Constantly it has been discussed, years and years.

DR. JAIN: If I quote from what we heard at the workshop from all the experts sitting there, if there is a two millimeter drop in mercury, and in the patient in the ICU, the first thing you go for is some sort of fluid. And if this is available on the floor, this is what would be given. So that is how widely it is used.

DR. ALVING: It is interesting. I think it is much more in the surgical world. The medicine, the intensivists wouldn't be the ones to --

DR. JAIN: They do use it in ICU. And in traumatic hemorrhagic patients. That is what we heard.

DR. RHEE: They don't use it too much in traumatic hemorrhagic patients. They use it in the ICU. There was a recent study done on a combination Hespan because they were using it with hypertonic saline. That is the last time we had a very large randomized prospective trial which was done, completed about a year ago. It is all published.

But we don't use it acutely in the trauma bay. I don't think anybody in the trauma community does that. But once you get into the ICU, or a lot of the anesthesiologists will use it in the operating room.

DR. EPSTEIN: I would also mention that Hextend is used by Department of Defense. It is in the medics' backpack.

DR. RHEE: I wrote the guideline for TCCC, and when I originally wrote it, I wrote it as a low volume for the medic so he wouldn't have to carry a little bit more weight. And it got blown way out of proportion. And what happened was, there was an argument for using a colloid,

because the 7.5 percent hypertonic saline was not made and manufactured by anybody.

We went for years trying to figure out how to go through the FDA process to get that made. No one knew where that would belong. Anyway, the Hespan was going to be used and then the paper came out which showed that Hextend might be a little bit better with the coagulopathy issue. So they went ahead and ruled for 500 cc's of Hextend. So it is in the TCCC guidelines for the military.

I yielded on that one point to get the rest of it through, which was to minimize using crystalloids, using hypertensive resuscitation plasma and all these other things. But what happened is, that even though it was in the guideline, the Special Operations carry it, but the rest of the military does not.

DR. HOLLINGER: Other questions? We are adjourned. Thank you all.

(Thereupon, at 4:11 p.m. the meeting was adjourned)